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PREPARATION AND PROPERTIES OF SOME

CYCLIC HYDROXYLAMINES

by

Ⓒ ABDEL-MONAEM M. K. EL-HAWARI

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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PHARMACEUTICAL SCIENCES

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and
recommend to the Faculty of Graduate Studies and Research, for
acceptance, a thesis entitled "Preparation and Properties of Some
Cyclic Hydroxylamines" submitted by Abdel-monaem M. K. El-hawari
in partial fulfilment of the requirements for the degree of Doctor
of Philosophy.

TO SOHA

ABSTRACT

The primary objective of the present study was to prepare some novel cyclic hydroxylamines and to study their chemical and pharmacological properties. Cyclic hydroxylamines have recently been shown to be metabolites of certain cyclic secondary amines. Little is known of their pharmacological properties.

Reductive cyclization of three 4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-ones by means of sodium borohydride and palladium-charcoal gave mainly spiro (1-hydroxyindoline)-2,4'-(1'-phenyl-1$\underline{H}$-pyrazolin-5'-ones) and 4-(2-aminobenzyl)-1-phenyl-2-pyrazolin-5-ones; the proportion of each depended on the solvent system used. Reduction of the 4-(2-nitrobenzylidene)pyrazolones with sodium borohydride yielded the corresponding nitrobenzyl derivatives. These were reduced further with several reducing systems giving different compounds including spiro(indoline)pyrazolones and pyrazolo-quinoline derivatives.

A study of the chemical reactivity of the isolated spiro-(N-hydroxyindoline)pyrazolones was undertaken. This included their reduction to the corresponding indolines, oxidation to 2-$\underline{H}$-indolenine 1-oxide and reactions with nucleophilic reagents, in acid media, to form 5-substituted indoline derivatives. Acetylation and methylation gave N-acetyloxy and N-methyloxy derivatives and, in addition, some rearrangement products. Other rearrangements also occurred when attempts were made to benzoylate and sulfonate one of these spiro-N-hydroxyindolines.

Catalytic hydrogenation of the 4-(2-nitrobenzyl)pyrazolones in several solvents gave different and unexpected products which were found to be spiro(tetrahydroquinoline)pyrazolone derivatives. The solvent was involved in their formation, for which a mechanism is suggested. Eighteen of these compounds were also prepared by condensation of 4-(2-aminobenzyl)-1-phenyl-2-pyrazolin-5-ones with appropriate aldehydes.

A reinvestigation of the nature of the products obtained by sodium borohydride and palladium-charcoal reduction of two 4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-ones has revealed that, contrary to literature reports, none of the products is a cyclic hydroxylamine. Instead, the products were found to be thiols which readily oxidized in air to spiro(benzothiazoline)pyrazolones. Attempts to isolate N-hydroxy compounds by the reduction of the 4-(2-nitrophenylthio)pyrazolones using different reducing systems failed.

Catalytic hydrogenation of the 4-(2-nitrophenylthio)pyrazolones did not produce spiro(dihydrobenzothiazine)pyrazolone derivatives. However, the latter compounds were readily obtained by the action of aldehydes on 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-ones.

The mass spectra of 1-hydroxy-2-phenyl-1,2-dihydropyridine and its O-benzoyl derivative as well as the mass spectra of three spiro(N-hydroxyindoline)pyrazolones, two O-acetyl derivatives and one O-methyl compound were recorded and interpreted. The N-hydroxy compounds demonstrated expulsions of ȮH radicals from the molecular ions. The loss of oxygen atoms and water molecules also occurred. The O-methyl compound showed an appreciable

expulsion of an OCH_3 radical from its molecular ion; $(M-59)^+$ and $(M-60)^+$ in the O-acetyl derivatives are due presumably to direct losses of a CH_3COO radical and a CH_3COOH molecule from the molecular ions.

Also, the mass spectra of six spiro(indoline)pyrazolones and two spiro(benzothiazoline)pyrazolones are discussed in detail. Their proposed fragmentations are substantiated by means of deuterium labelling and accurate mass measurements. All these compounds gave abundant molecular ions which fragmented mainly by the expulsions of CO and PhNCO molecules. Decomposition of the (M-CO) ions gave rise to many of the prominent fragments in the spectra.

In addition to the above compounds, the mass spectra of four simple pyrazolones, including the medicinal compounds antipyrine and aminopyrine, were recorded and interpreted. All these spectra contained several ions resulting from initial N-N bond cleavages; such a fragmentation has not been reported to occur in the pyrazolone nucleus. Strong ions at m/e 56 were found in the spectra of antipyrine and aminopyrine and also in some other 2,3-dimethyl pyrazolone derivatives prepared in this study; this ion could be of diagnostic value.

Some selected examples of the compounds prepared in this study, including two of the spiro(N-hydroxyindoline)pyrazolones were evaluated for neuroleptic and analgesic activity. The N-hydroxy-indolines had only very weak sedative properties (p.o. or i.p.) and no analgesic activity (p.o.) at dose levels examined. The corresponding spiro(indoline) pyrazolones showed some neuroleptic and analgesic properties while 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one showed mild hypnotic effects.

ACKNOWLEDGEMENTS

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PREAMBLE

The ultimate aim of the proposed research was the synthesis of novel cyclic hydroxylamines, a study of their chemical reactions and a preliminary investigation of their pharmacological properties. Information on cyclic hydroxylamines is scattered throughout the scientific literature but the topic has not been reviewed. Consequently, it was considered necessary to compile a detailed review of the pertinent literature on these compounds and the introduction which follows is devoted entirely to this purpose.

During the course of the research described in this thesis, compounds other than cyclic hydroxylamines were also prepared and characterized. Relevant literature information on these compounds is included in the discussion section of the thesis.

CYCLIC   HYDROXYLAMINES

1.   INTRODUCTION

The structure of cyclic hydroxylamines (which will be also referred to as cyclic N-hydroxy compounds) may be represented as in (1). These compounds are disubstituted hydroxylamines (2) in which the N-hydroxy function is incorporated within a cyclic system.

(1)   (2)   (3)
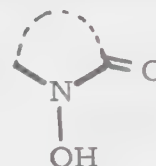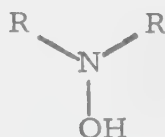
Although cyclic hydroxamic acids (3) are also cyclic N-hydroxy compounds, no attempt will be made to include them in the following discussion since they have recently been reviewed by several workers (Coutts, 1967; Bapat et al, 1969).

Simple examples of cyclic hydroxylamines are N-hydroxy-pyrrolidine (4), N-hydroxypyrazoles (5) and N-hydroxyisoxazolidine (6) to which reference will be made later in this introduction. In

(4)   (5)   (6)
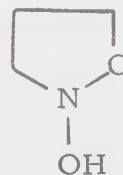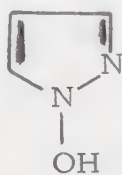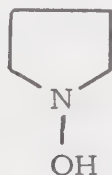
certain instances, cyclic N-hydroxy compounds exist in tautomeric equilibrium with a corresponding N-oxide (e.g. 7a ⇌ 7b), and the presence of one or both of these tautomers is dependent on the overall nature of the molecule. Some aspects of this tautomerism

(7a)   (7b)

will be discussed in detail later.

Until the beginning of the last decade, very little attention
was paid to the chemistry and biochemistry of hydroxylamines.
Recent studies have been generally confined to aromatic hydroxyl-
amines especially those found to be metabolites of carcinogenic
amines.   A comprehensive review of the chemistry of aliphatic and
aromatic hydroxylamines, which also included some cyclic hydroxyl-
amines, was recently published by German authors (Zeeh and Metzger,
1971).   Also, Weisburger and Weisburger (1973) briefly summarized
the chemistry of these compounds in their discussion which dealt
mainly with the biochemical formation as well as pharmacological and
toxicological properties of hydroxylamines and hydroxamic acids.

Some reasons for studying the chemical and biological
properties of cyclic hydroxylamines are now suggested:
(a)   More knowledge of the chemistry of these compounds is required
in order to help understand the recent flood of biochemical studies in
this area.   N-hydroxylation, especially of free and N-acyl aromatic
amines, is now a well recognized metabolic pathway (Irving, 1970;
Weisburger and Weisburger, 1973).   Like other hydroxylated
metabolites, N-hydroxy derivatives are subject to further metabolic
conversions such as conjugation with glucuronic, sulfuric and perhaps
phosphoric acid, and reduction.   The N-hydroxy metabolites are

often reactive and generally more toxic than their parent amines. In
, vitro, they can combine as such, or after further reactions, with
essential life supporting molecular species. Current studies suggest
that metabolic N-hydroxylation of certain aromatic amines produces
potentially carcinogenic (Miller, 1970; Gutmann et al, 1969), muta-
genic (Miller and Miller, 1971) and nephrotoxic (Calder et al, 1973)
products.

Until recently, biochemical N-hydroxylation studies were
mostly confined to aromatic amines especially those which demon-
strated carcinogenic activity. Some aliphatic amines were also
studied but relatively little success was achieved in demonstrating
N-hydroxylation. Beckett and Al-Sarraj (1972), however, showed
that certain aliphatic amines do yield hydroxylamines, metabolically.
So do secondary amines in which the nitrogen atom is a part of the
ring system. Compounds based on the piperidine (8), morpholine (9)
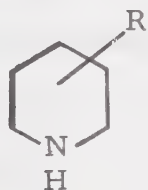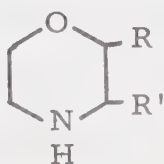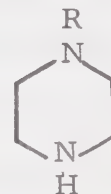
(8)   (9)   (10)

and piperazine (10) structures were found to be metabolized in vitro to
the corresponding hydroxylamines. One of these, phenmetrazine (11)
has been shown to oxidize to N-hydroxyphenmetrazine (12) in vivo in
various animals. It was also shown (Beckett and Al-Sarraj, 1972)
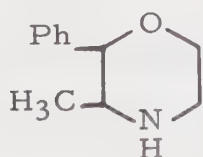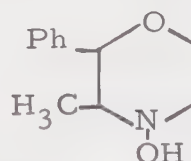
(11)   (12)

that compounds structurally more complex than (8) also form hydroxyl-
amines metabolically. For example, pipradol, normorphine, nor-
codeine and nortriptyline are metabolized to their corresponding
hydroxylamines. It is not yet known, however, whether metabolic
N-hydroxylation of all these compounds increases toxicity or whether
it is sometimes a detoxification reaction.

(b) In addition to this flow of biochemical work, numerous reports on
the pharmacological activity of cyclic N-hydroxy compounds have
recently started to appear in the literature. Although studies in this
area were limited and the early results were not outstanding (Johns
and Major, 1927; Mamalis, 1971), recent studies describe diverse
activities such as analgesic, adrenolytic, tranquilizing, muscle
relaxant, anticonvulsant, antimicrobial and antiprotozoal properties
for this type of compound.

Some α- and β-1-alkoxy-3-methyl-4-phenyl-4-propion-
oxypiperidines (13) were synthesized by Major and Dursch (1961) and
examined for analgesic activity in rats. Two of these compounds
(13, R=CH$_3$ or C$_2$H$_5$) showed strong oral activity but also many toxic
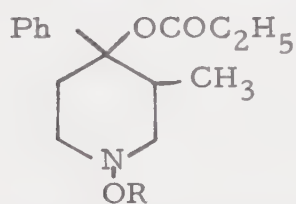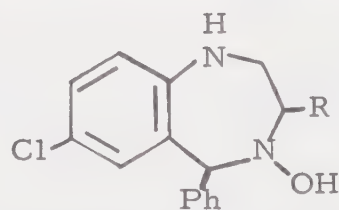
(13)   (14)

manifestations. N-hydroxybenzodiazepine derivatives such as (14)
have been screened for potential central nervous system (C.N.S.)
depressant activity (Grindstedvaerket, 1967). Some related N-hydroxy-
benzodiazepines were also evaluated as anticonvulsants (Hoffman-
LaRoche, 1966).

The N-hydroxyindole derivatives (15) were found to possess C.N.S. depressant as well as adrenolytic activity (Petracek, 1967). N-alkyloxybenzimidazole derivatives (16) also showed C.N.S. depressant, muscle relaxant and tranquilizing properties (Ciba, 1966; DeStevens et al, 1967). A variety of related compounds such as

(15)   (16)
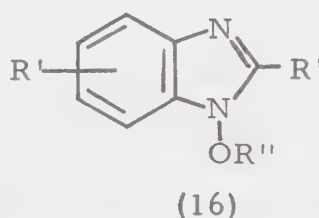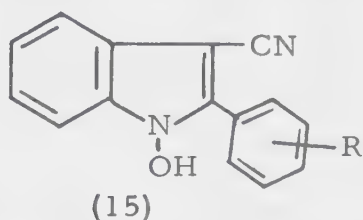
O-ethers of 1-hydroxyindoles and 1-hydroxybenzimidazole 3-oxides were found to be generally less active than (16) (DeStevens et al, 1967).

The antimicrobial properties of some O-ethers of 4,6-diamino-1,2-dihydro-1-hydroxy-1,3,5-triazines (17) were described by Mamalis et al (1965). These compounds were found to be active in vitro against a wide range of bacteria. Later investigations showed that these ethers possessed unexpected antimalarial properties

(17)
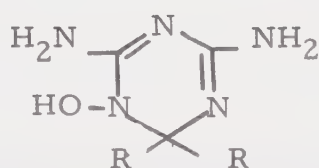
even against resistant strains of Plasmodium berghei. A related bis-triazine ether also showed trypanocidal activity of a high order in mice (Mamalis, 1971).

(c) The recent isolation of some derivatives of cyclic hydroxylamines from some plant and animal species demonstrated that these compounds exist in nature and stimulated further chemical and biological interest

in cyclic hydroxylamines. All compounds isolated are derivatives of indole. A glucoside (18) which was named neoglucobrassicin was isolated from Brassica napus L. var. napobrassica (Gmelin and

(18)
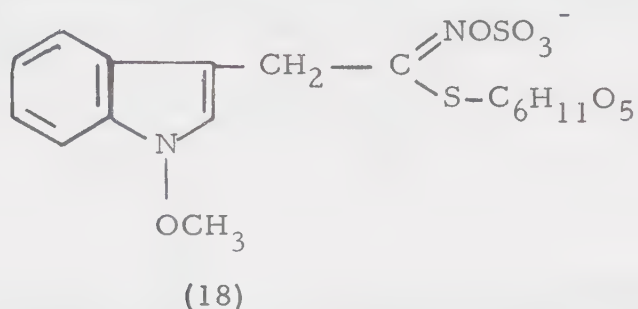
Virtanen, 1962). This glucoside was identified on the basis of products formed from enzyme cleavage, acid hydrolysis and hydrogenolysis with Raney nickel.

Subsequently, a tryptamine alkaloid, 1-methoxy-3-(2-dimethylaminoethyl)indole (19) which was given the name lespedamine was isolated from the leaves of Lespedeza bicolor var. japonica (Morimoto and Oshio, 1965). A related N-methoxyindole derivative

(19)   (20)
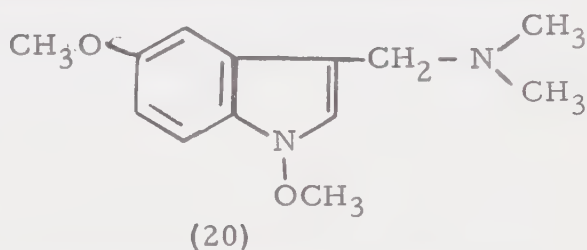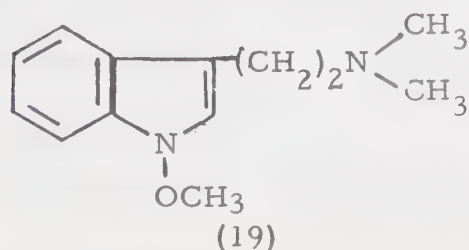
identified as 1,5-dimethoxy-3-dimethylaminomethyl)indole (20) was found to be the major alkaloid in Gymnacranthera paniculata var. zippeliana, (Johns et al, 1967). Both (19) and (20) were identified by their spectra and by their ease of reduction to the corresponding amines (NH for $N-OCH_3$).

In addition to these plant products, chemical studies on luciferin, a crystalline substance isolated from the firefly, Cypridina hilgendorfii, indicated that it was an N-hydroxyindole derivative (21)

(Hirata et al, 1959; Shimomura, 1960).

(21)
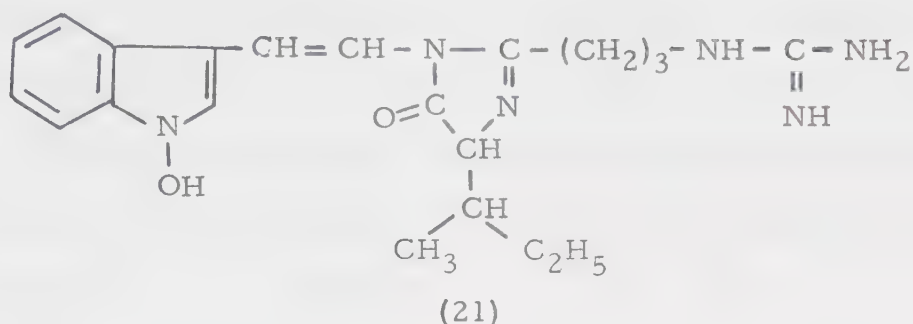
2. PREPARATION OF CYCLIC HYDROXYLAMINES

Cyclic hydroxylamines have been prepared by various methods from a variety of precursors. These methods are conveniently grouped together for discussion in the following sections:

A) Preparation of cyclic hydroxylamines by direct N-oxidation of the corresponding amines.

B) Reduction of cyclic nitrones

C) Addition to cyclic nitrones

D) Formation of cyclic hydroxylamines by reductive or non-reductive cyclization reactions.

E) Miscellaneous preparations.

(A) Direct N-Oxidation of Secondary Cyclic Amines:

Reactions of this type are rarely used for the preparation of cyclic hydroxylamines, possibly due to the expected side reactions which might accompany the N-oxidation process. However, this method can be useful for the preparation of certain N-hydroxy compounds which might be difficult to obtain by other synthetic routes.

In most of these reactions hydrogen peroxide is employed with or without a catalyst as the oxidizing agent. 1-Hydroxymorpho-

line (22) was obtained by the oxidation of morpholine with different

concentrations of hydrogen peroxide but the yields were generally

poor (Henry and Dehn, 1950; Blout et al, 1958; Zinner and Kliegel,

1966). 1-Hydroxypiperidine (23) and 1-hydroxypyrrolidine (4) were

similarly prepared (Blout et al, 1958). An attempt (Thesing and

(22)   (23)   (4)
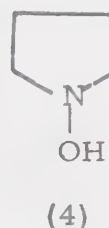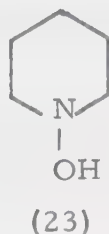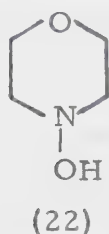
Sirrenberg, 1959) to improve the yield of these compounds by

catalysing the reaction with methyl formate was unsuccessful but

formic acid (Ruppert, 1960) and silicotungestic acid (Kawaguchi et al,

1967) were successfully used for this purpose.

An early report (Ingraffia, 1933) that indole-magnesium

bromide reacted with hydrogen peroxide to give 1-hydroxyindole was

recently discounted by Kawana et al (1965). These investigators and

others (e.g. Habib and Rees, 1962) failed to oxidize some cyclic

amines to the corresponding hydroxylamines by means of hydrogen

peroxide. Similarly, no cyclic N-hydroxy compounds were formed

when ferric chloride was used (Dobeneck and Lehmerer, 1957;

Kawana et al, 1965) although Houff et al (1954) reported earlier the

oxidation of indole-3-acetic acid to the corresponding N-hydroxyindole

using this reagent.

The use of percarboxylic acids for the N-oxidation of

tertiary amines is very common and a considerable number of N-oxides

have been prepared by this method. Recently, Beckett and Salami

(1972) claimed that one of these acids (m-chloroperbenzoic acid)

successfully oxidized phenmetrazine (11) to 1-hydroxyphenmetrazine

(12). An earlier attempt (Stacy et al, 1964) to use percarboxylic

acids for the preparation of 1-hydroxy-2-phenylbenzimidazole from

the corresponding amine failed. The related compound, 2,6-dimethyl-

benzimidazole (24) was said to be oxidized by bromine to the corres-

ponding hydroxylamine (25) (Niementowski, 1892).

$$Br_2/H_2O$$

(24)   (25)
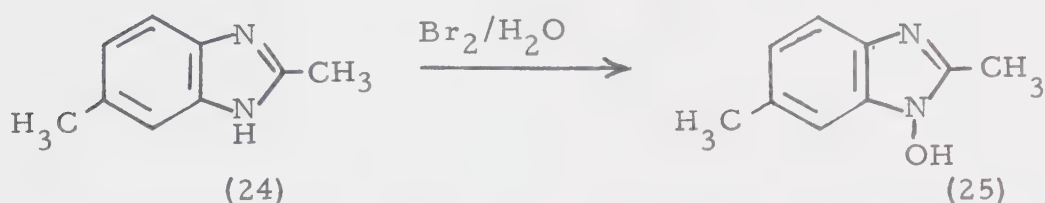
N-Acetoxy and N-benzoyloxypiperidines (27) can be

prepared from piperidine (26) by the action of acetyl and benzoyl

peroxides respectively (Gambarian, 1925; Gambarian and Kazaryan,

1933). 1-Benzoyloxy-2,2,6,6-tetramethylpiperidine (28) and

$$(RCOO)_2$$

R = CH$_3$ or ph

(26)   (27)
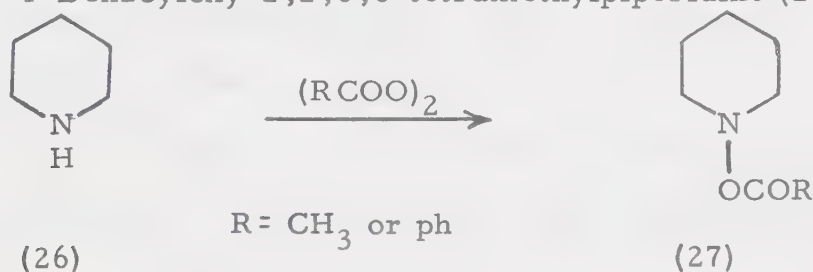
1-benzoyloxy-2,2,5,5-tetramethylpyrrolidine (29) were similarly

prepared. Hydrolysis of (28) and (29) gave rise to the corresponding

(28)   (29)
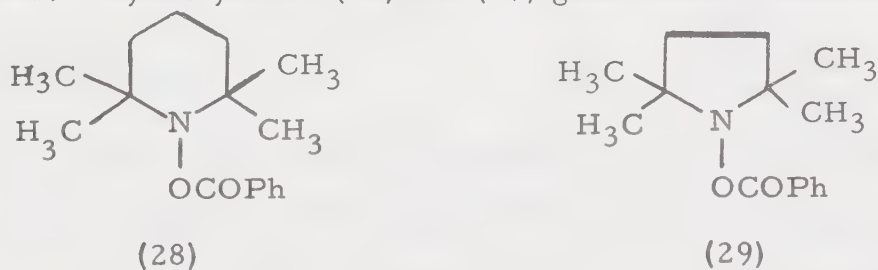
N-hydroxy compounds (Feldman and Hoffmann, 1964).

(B) Reduction of Cyclic Nitrones

Reduction of nitrones (30) to the corresponding secondary

amines (33) can proceed by two different pathways. The intermediate

imines (31) or hydroxylamines (32) have been isolated. Deoxygenation
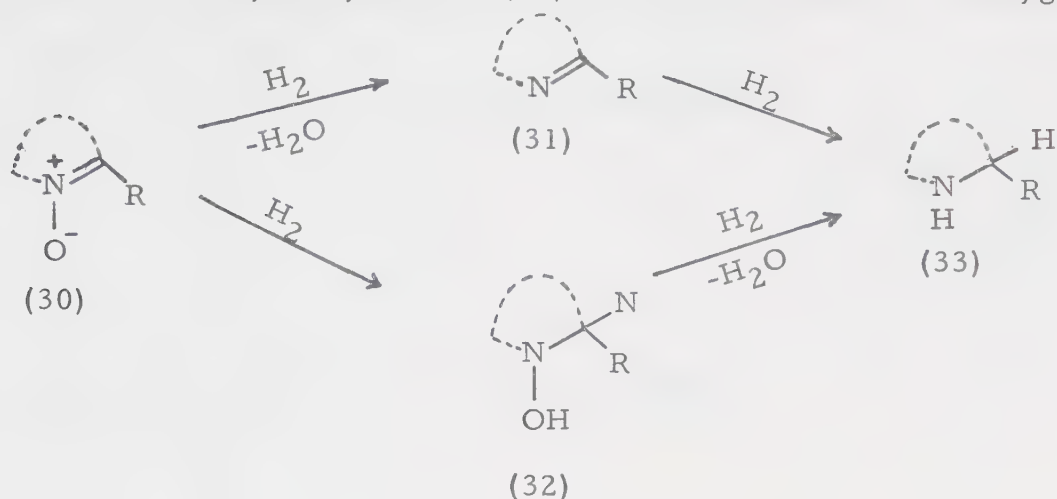
to (31) is generally effected by using triphenylphosphine, phosphorous

trichloride, phosphorous oxychlorides, sulfur dioxide, zinc and acetic

acid as well as catalytic hydrogenation. Zinc and mineral acids

reduce the nitrone group to the secondary amine stage (33). Reduc-

tions with complex metal hydrides lead, in most cases, to the forma-

tion of hydroxylamines.

1,5-Dihydroxy-3,3-dimethylpiperidine (35) was prepared by

the reduction of (34) using potassium borohydride (Brown et al, 1959).
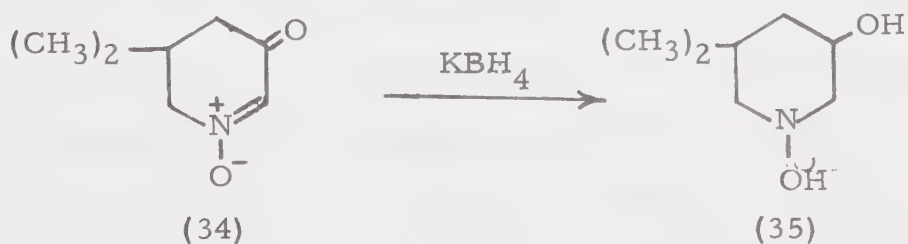
The same reagent was used for the reduction of Δ'-pyrroline 1-oxides

to the corresponding 1-hydroxypyrrolidines (Bonnett et al, 1959).

The N-hydroxybenzodiazepine (14, R=H) was prepared by

reducing nitrones (36) or (37) with sodium borohydride in ethanol or

diglyme. Reduction of the latter was accompanied by cleavage of

the aziridine ring (Field et al, 1966). These reactions were also

effected by using tetramethylammonium borohydride (Hoffmann-

(37)

NaBH$_4$/Diglyme

(36)

NaBH$_4$/EtOH

(14)

LaRoche, 1966).

The use of lithium aluminum hydride for the reduction of cyclic nitrones to the corresponding hydroxylamines was first reported by Exner (1955). There have been claims that reduction stops at the hydroxylamino- stage even when excess reagents and fairly vigorous conditions are used (Thesing and Sirrenberg, 1959). Among N-hydroxy compounds prepared in this way are 1-hydroxypyrrolidine from $\triangle^{1}$- pyrroline 1-oxide (Thesing and Sirrenberg, 1959) and 7-chloro-4- hydroxy-5-phenyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (39) from the nitrone (38) (Sulkowski and Childress, 1963). 7-Chloro-2- methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine

(38)

LiAlH$_4$

Et$_2$O

(39)

was prepared similarly (Sternbach and Reeder, 1961).

The dimeric 1,2,3,4-tetrahydropyridine 1-oxide (40) did

effected by using tetramethylammonium borohydride (Hoffmann-

(37)

NaBH$_4$/Diglyme

(14)

(36)

NaBH$_4$/EtOH

LaRoche, 1966).

The use of lithium aluminum hydride for the reduction of cyclic nitrones to the corresponding hydroxylamines was first reported by Exner (1955). There have been claims that reduction stops at the hydroxylamino- stage even when excess reagents and fairly vigorous conditions are used (Thesing and Sirrenberg, 1959). Among N-hydroxy compounds prepared in this way are 1-hydroxypyrrolidine from $\triangle^1$- pyrroline 1-oxide (Thesing and Sirrenberg, 1959) and 7-chloro-4- hydroxy-5-phenyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (39) from the nitrone (38) (Sulkowski and Childress, 1963). 7-Chloro-2- methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine

(38)

LiAlH$_4$

Et$_2$O

(39)

was prepared similarly (Sternbach and Reeder, 1961).

The dimeric 1,2,3,4-tetrahydropyridine 1-oxide (40) did

not react with lithium aluminum hydride. However, it could be

reduced catalytically over platinum in acidic methanol to give 1-

hydroxypiperidine (23) (Thesing and Mayer, 1956). Catalytic hydro-

genation of the trimer (41) afforded the same N-hydroxy compound

(40)

H₂ Pt

H₂
cat.

(41)

(23)
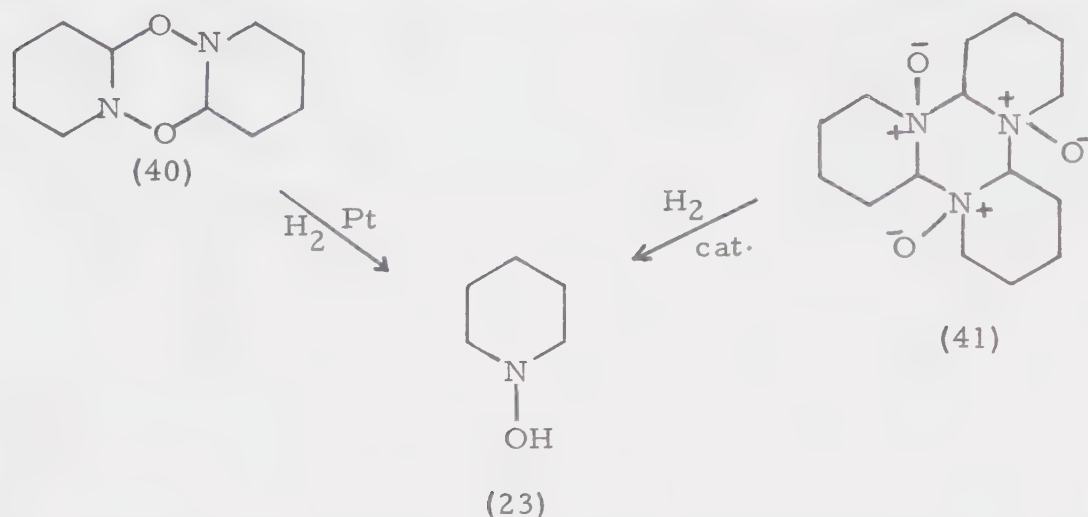
(Thesing and Mayer, 1957). The dimeric nitrone (42) was also

hydrogenated in the presence of Adam's catalyst to give 1,8-dihydroxy-

1,8-diazacyclotetradecane (43). Further hydrogenation of (43) over

Raney nickel yielded the corresponding amines (Alford et al, 1966;

Rogers, 1956).

$CH \cdot [CH_2]_5$

H_2/PtO

$[CH_2]_6$

$^-O-N+$

$+N-O^-$

$HO-N$

$N-OH$

$[CH_2]_5 \cdot CH$

$[CH_2]_6$

(42)

(43)
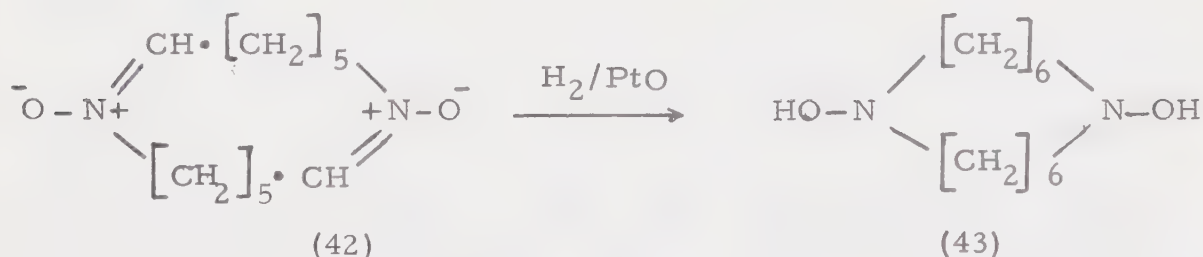
More powerful chemical reagents are employed occasionally

for the reduction of nitrones to hydroxylamines. The N-hydroxyisox-

azoline (45) was formed when the isoxazoline 1-oxide (44) was reduced

with zinc and acetic acid or with sodium iodide and acetic acid (Kohler

and Barrett, 1926). The N-hydroxytetrahydroquinoline (47) was also

prepared by the zine and acetic acid reduction of (46) (Taylor and

(44)   (45)

and Kalenda, 1953). In contrast, the dioxide derivatives (48) were

(46)   (47)
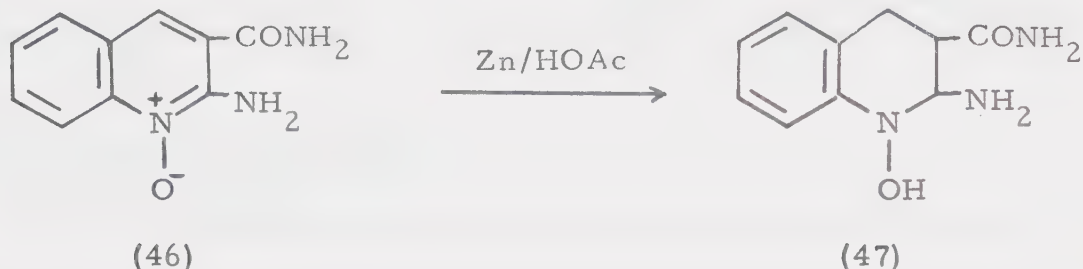
reduced with sodium hydrosulfite to 1,4-dihydroxypyrazoles (49) but

when reduction was performed with zinc and acetic acid, 4-hydroxy-

pyrazoles (49, N-H for N-OH) were formed (Freeman et al, 1969).

(48)   (49)
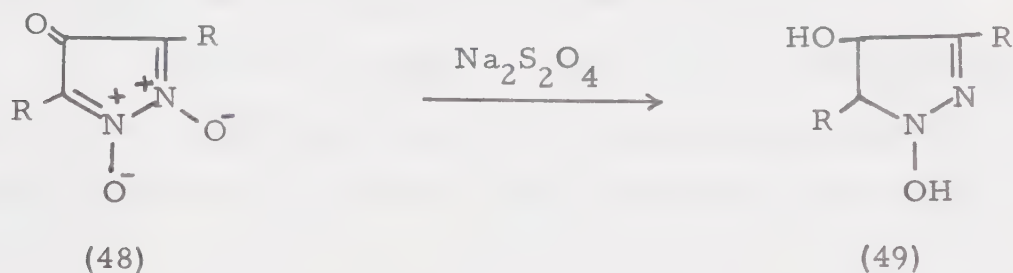
Reduction of the cyclic nitrone (50) was accompanied by an

elimination of methyl alcohol and yielded the 1-hydroxypyrrole (51).

This reduction was achieved using sodium-potassium alloy, alkyl or

aryl magnesium bromides (Blatt, 1934). Sodium-potassium alloy was

(50)   (51)
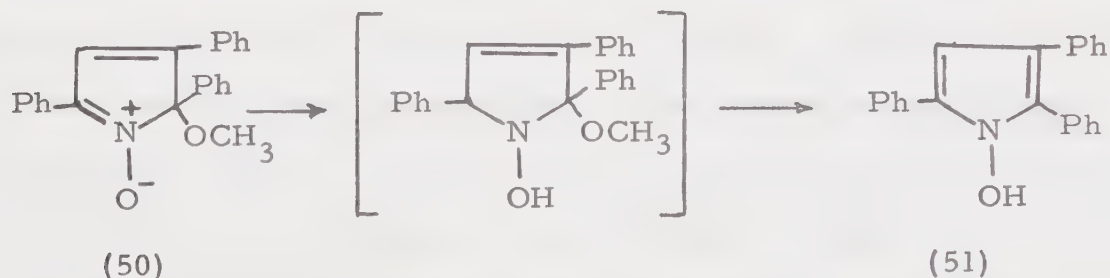
also reported to reductively dimerize 5,5-dimethyl-Δ'-pyrroline

1-oxide (52) to the 1,1'-dihydroxy-2,2'-bipyrrolidinyl derivative (53) (Clark et al, 1959).

(52)   (53)
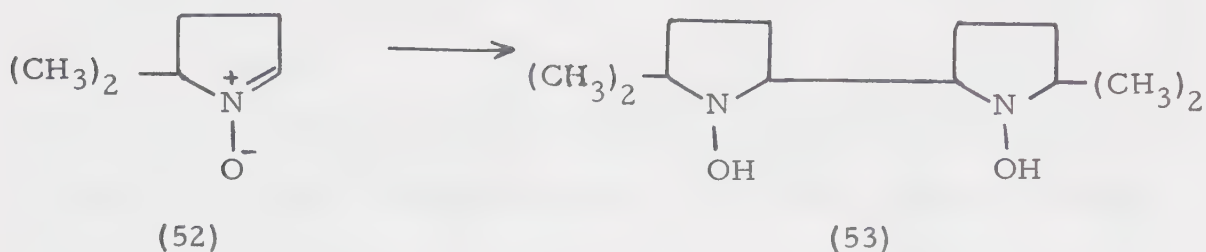
(C)   Addition to Cyclic Nitrones:

Grignard reagents add across the double bond of cyclic nitrones leading, in certain instances, to the formation of stable cyclic hydroxylamines. Some α-alkyl and α-aryl N-hydroxy compounds were prepared in this way from pyrrolidine 1-oxides, piperidine 1-oxides, pyridine 1-oxides and quinoline 1-oxides.

1-Hydroxy-2-phenylpyrrolidine (55) was the product of the reaction of Δ'-pyrroline 1-oxide (54) and phenylmagnesium bromide (Thesing and Sirrenberg, 1959). Other N-hydroxypyrrolidines are

(54)   (55)
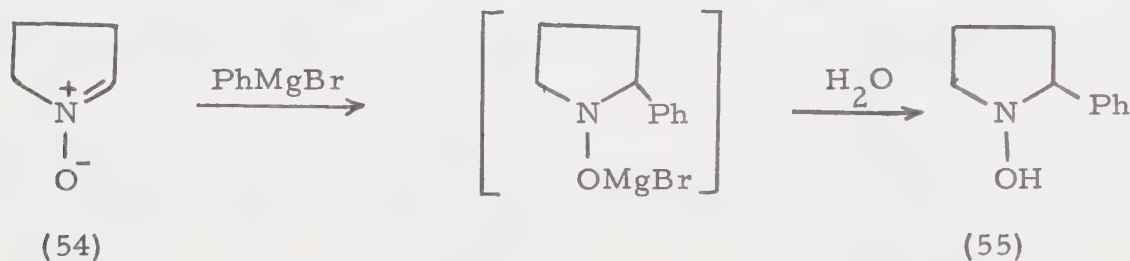
prepared similarly (Bonnett et al, 1959; Delpierre and Lamchen, 1963). The tetrahydropyridine 1-oxide dimer (40), which is resistant to a number of nitrone reactions such as reduction with lithium aluminum hydride or with sulfur dioxide, reacted readily with phenylmagnesium bromide to give 1-hydroxy-2-phenylpiperidine (Thesing and Mayer, 1956, 1957).

2,2-Diphenyl-3-oxo-1-hydroxyindoline (57) was formed from the reaction of 2-phenylisatogen (56) and phenylmagnesium

bromide (Rugguli and Casper, 1939). The latter reagent also reacted

(56)

(i) PhMgBr
(ii) H_2O

(57)
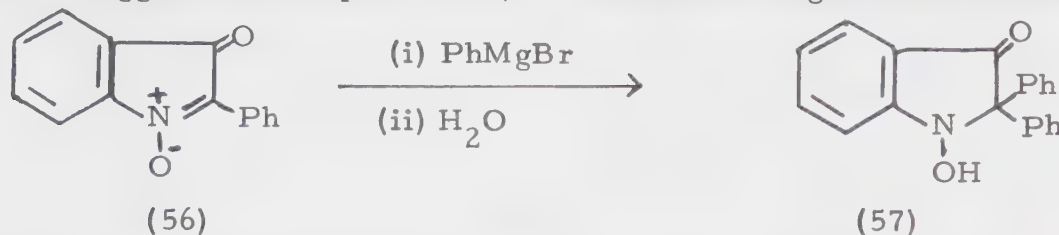
with the cyclic N-oxide (58) to yield 7-chloro-4-hydroxy-5-phenyl-1,3,
4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (59) (Grindstedvaerket)
1967).

(58)

(59)

Addition of Grignard reagents to pyridine 1-oxides and
quinoline 1-oxide generally gives α-alkyl and α-arylpyridines
quinolines (Colonna, 1936; Ochiai and Arima, 1950). In some
instances, the intermediates (60) are also oxidized by the unreacted
N-oxides in the reaction mixture to form α-substituted N-oxides
(Colonna and Risaliti, 1954; Kato and Yamanaka, 1965). When these
reactions were carried out in tetrahydrofuran, the intermediates (60)

(60)
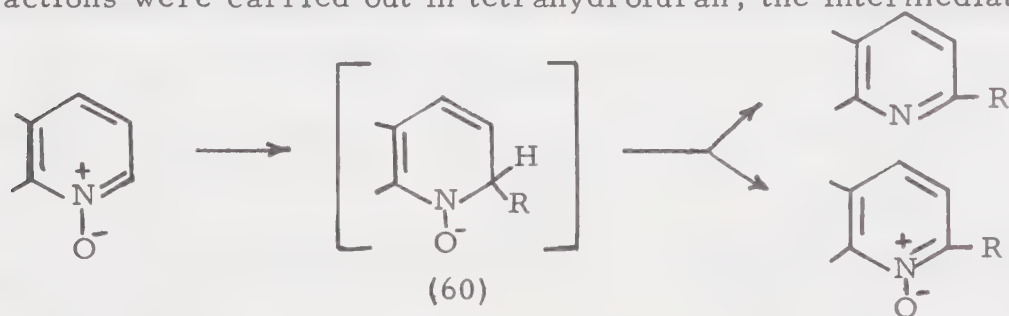
afforded cyclic N-hydroxy compounds. Thus, 1-hydroxy-2-phenyl-
1,2-dihydropyridine (62a), its 6-methyl derivative (62b) and 1-hydroxy-
2-phenyl-1,2-dihydroquinoline were obtained by the reaction of phenyl-
magnesium bromide with pyridine 1-oxide, 2-picoline 1-oxide and
quinoline 1-oxide respectively. Attempts to repeat this reaction with

a, R=H
b, R=CH₃

(61)   (62)
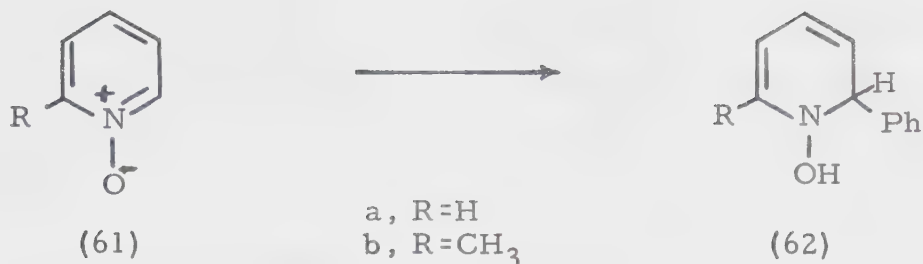
4-substituted quinoline 1-oxides failed to yield any N-hydroxy
compounds (Kato and Yamanaka, 1965).

Hydrogen cyanide is reported to add across the double
bond of nitrones giving adducts which generally lose water in the
presence of bases.   This reagent, however, reacted with the pyrroline
1-oxides (63) to give 2-cyano-1-hydroxypyrrolidines (64) which were
stable to alkali but readily oxidized to the cyanonitrones (65) (Bonnett
et al, 1959).   Cyclic nitrones also react with active hydrogen

(63)   (64)   (65)
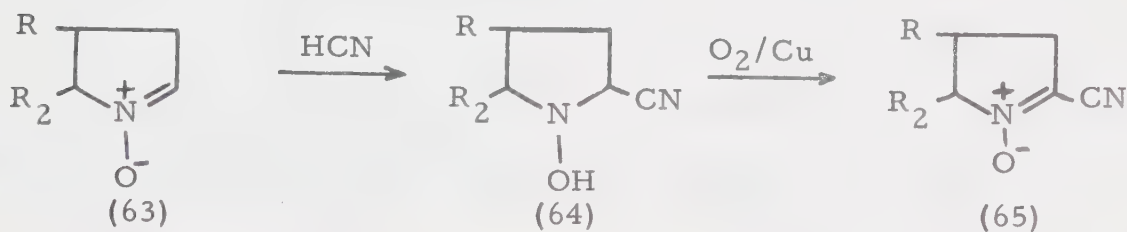
compounds forming simple adducts.   For example, treating pyrroline
1-oxides such as (52) with nitromethane, in the presence of base,
yielded the 2-nitromethyl-1-hydroxypyrrolidine (66) (Bonnett et al,

(52)   (66)
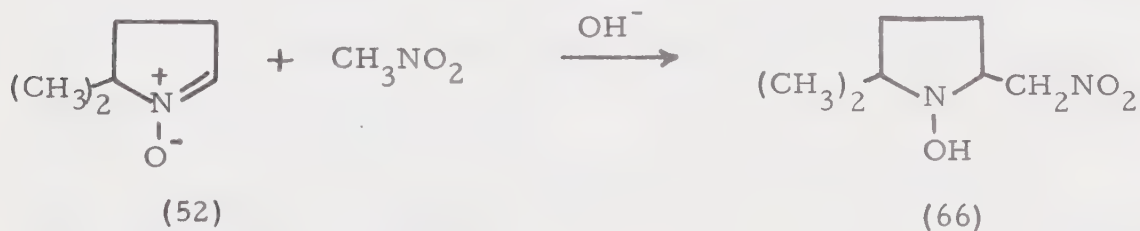
1959; Bowering et al, 1963).

Some nitrones undergo aldol-type reactions, 2,4,4-Tri-
methyl-Δ'-pyrroline 1-oxide (67), for example, dimerizes slowly on
standing to give the nitrone-hydroxylamine (68) (Brown et al, 1959a).

(67) → (68)
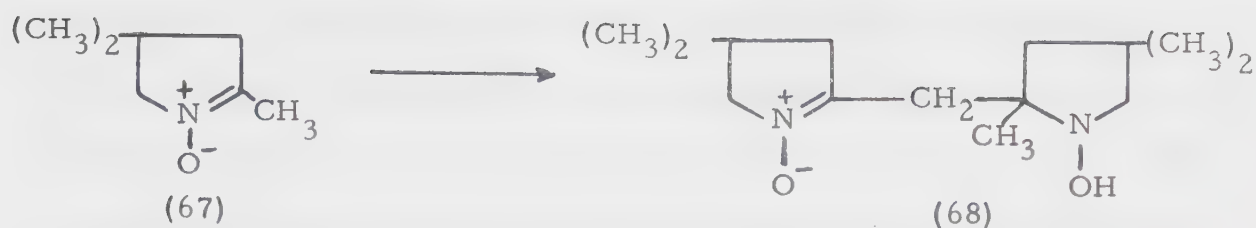
Dimerization was also induced and controlled by basic catalysts. Thus, the nitrone (52) is stable at room temperature but readily dimerizes under basic conditions. In the presence of triphenylmethyl sodium, an aldol-type reaction occurred leading to the bipyrrolyl derivative (70) while a benzoin-type dimerization to (69) occurred with sodamide in liquid ammonia. Sodamide in triethylamine gave a mixture of both dimers (Brown et al, 1959b, 1959c). The benzoin-type
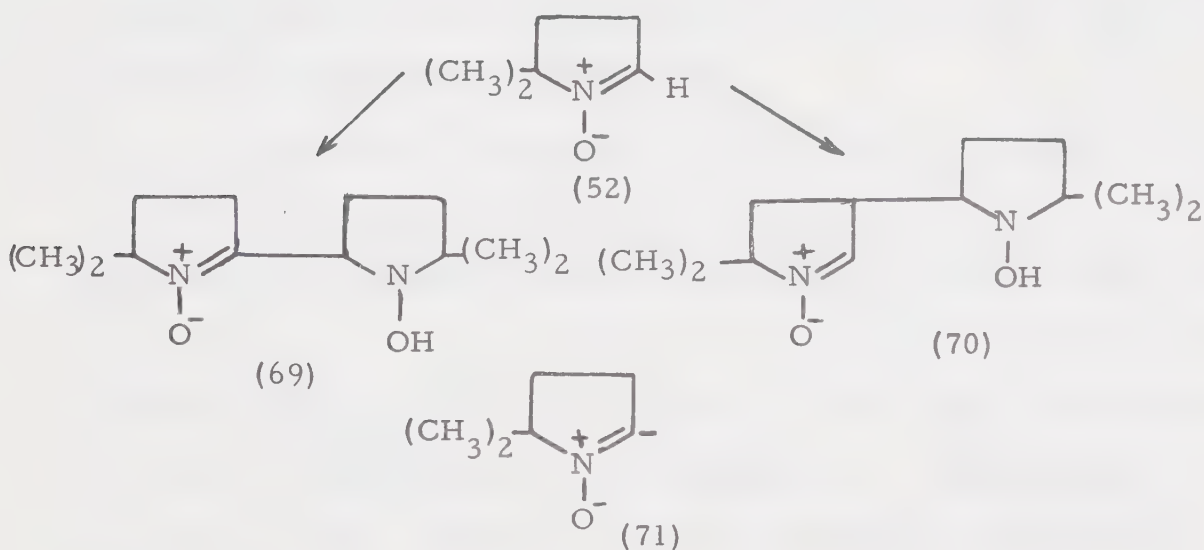
dimerization might be initiated by deprotonation of (52) to form the anion (71) (Brown et al, 1965).

(D) Cyclization Reactions:

The majority of cyclic hydroxylamines reported in the literature were prepared by cyclization reactions which involve either condensation of two molecules or the intramolecular cyclization of a single compound. These reactions generally utilize nitro or oxime

derivatives. Nitroso and hydroxylamino compounds are possible
intermediates in many cases and are sometimes used as initial reagents.
The mechanisms of these cyclization reactions are seldom clear and
accordingly the discussion of these mechanisms is mostly speculative.

Most often, especially when nitro compounds or oximes
are used, an initial reductive step is required prior to cyclization and
numerous reducing systems have been employed for this purpose.
However, the nitro group may also cyclize without initial reduction to
the nitroso or hydroxylamino stages. This alternative route involves
nucleophilic attack on the nitrogen atom of the nitro-group; the
attacking nucleophile can be an aliphatic carbanion, a reactive aromatic
ring or an amino group. These types of reactions were extensively
reviewed by London and Tennant (1964).

Cyclization reactions discussed now are classified under
two subheadings, reductive and non-reductive cyclizations. In the
first, a reducing agent is used, mainly to effect reduction of the oxime
or nitro-group to a hydroxylamino or nitroso function. The second
group includes those reactions in which the nitro-group's demand for
electrons is supplied from within the molecule. Miscellaneous
reactions in which cyclization involves quite different mechanisms
will also be reviewed.

i - Reductive cyclizations:

Various reducing agents have been employed for
the reductive cyclization of oximes and nitro compounds. These
reducing agents are generally mild although, in some cases, strong
reduction systems give rise to the required N-hydroxy compounds.

Zinc and ammonium chloride have been used by several

investigators for the preparation of aromatic hydroxylamines from the
corresponding nitro compounds. Reduction of o-nitrobenzyl ketones
(72) with this system was also successful and resulted in the formation
of the tautomeric 1-hydroxyindoles (7a ⇌ 7b). The hydroxylamine (73)
was postulated as an intermediate. The same synthetic route was

(72)   (73)

(7a)   (7b)
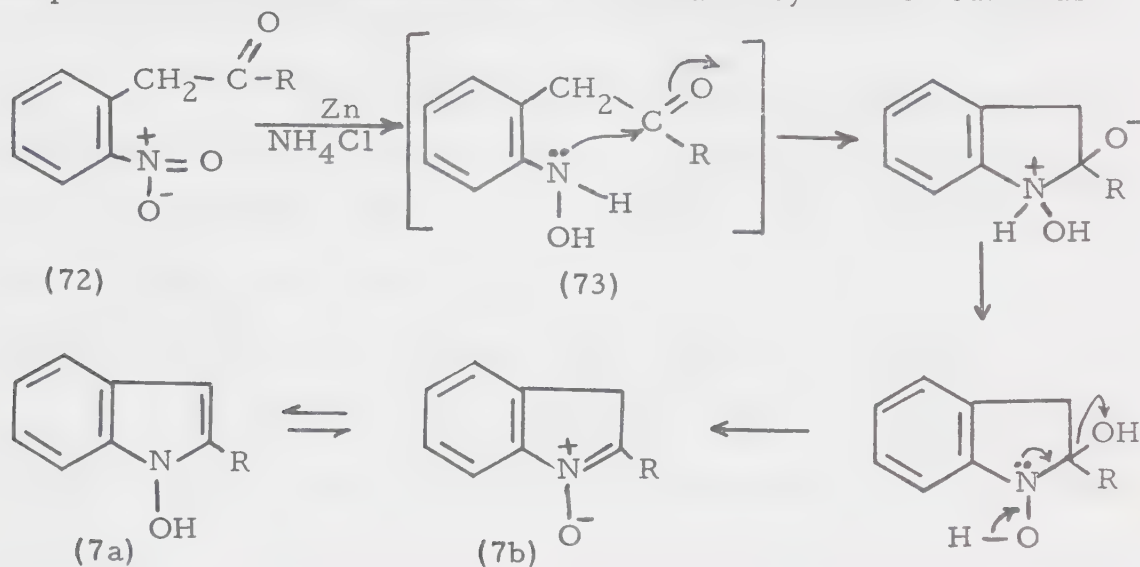
employed in an attempt to prepare the parent N-hydroxyindole, but it
led instead to a dimer formulated as (75) (Mousseron-Canet and Boca,
1965).

(74)   (75)
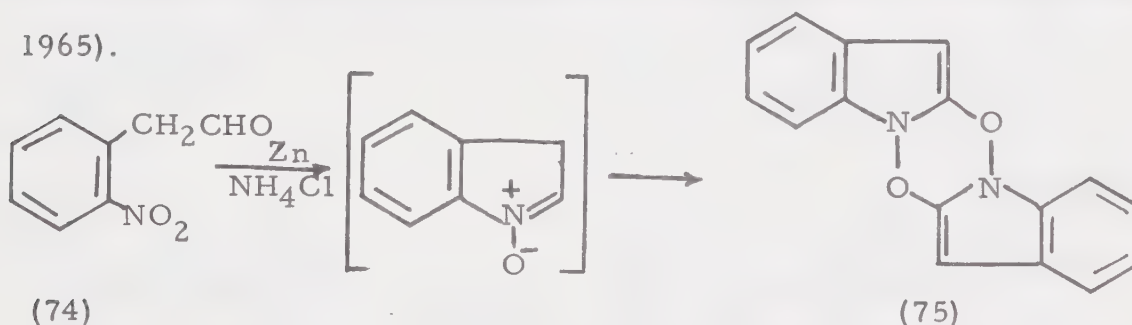
Reduction of 2-nitrophenylpyruvic acid (76) with sodium-
amalgam offered a means of preparing 1-hydroxyindole-2-carboxylic
acid (77) (Reissart, 1897). Similar results were obtained when
4-methyl-2-nitrophenylpyruvic acid was reduced. Reduction of (76)
with zinc and acetic acid yielded indole 2-carboxylic acid.

The same N-hydroxyindole (77) was the sole acidic
product obtained by the sodium borohydride/palladium-charcoal

(76) ⟶ (77)
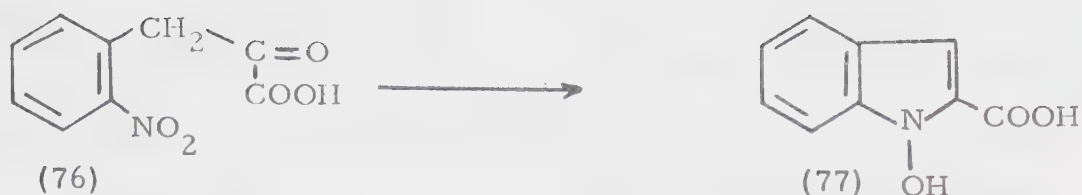
reduction of 2-nitrophenyl pyruvic acid (76) or its methyl ester; from
the latter a better yield was obtained (Coutts and Wibberley, 1963).

Catalytic hydrogenation of the oxime, semicarbazone and
phenylhydrazone of 2-nitrophenylpyruvic acid (76) over platinum or
palladium provided another route to 1-hydroxyindole-2-carboxylic
acid (77) (Baxter and Swan, 1967). Varying amounts of indole-2-
carboxylic acid were also formed along with the hydroxyindole.

Another example of the use of catalytic hydrogenation for
preparing cyclic hydroxylamines was reported earlier by Krajcinoric
and Vranjican (1933). Hydrogenation of acetyonylacetone dioxime (78)
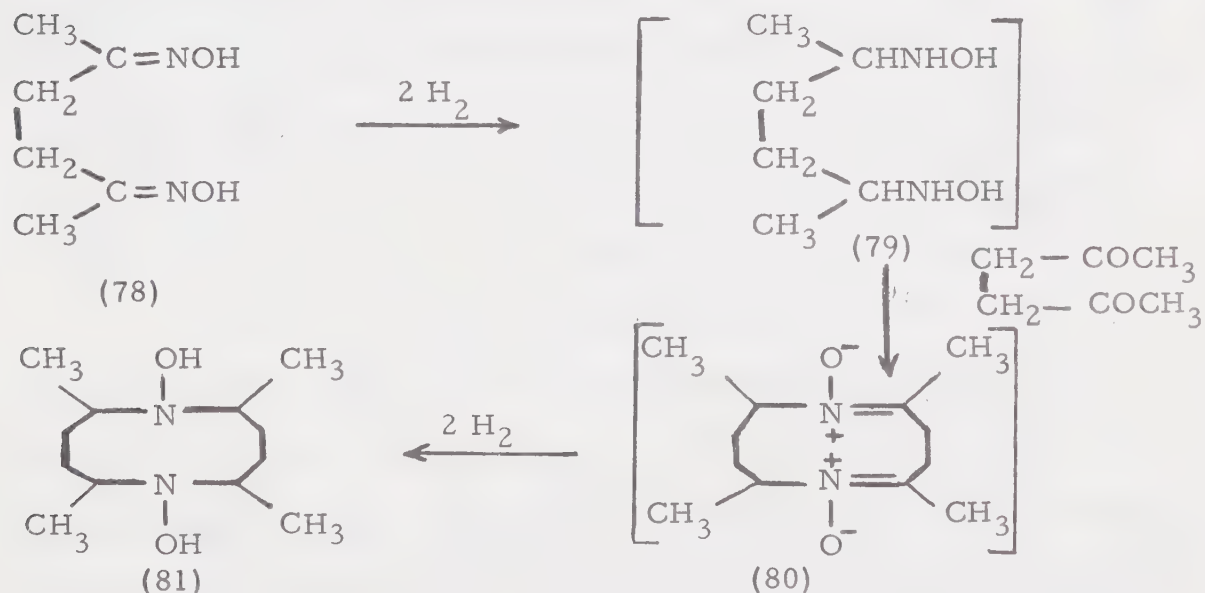
in acidic medium produced 1,6-dihydroxy-2,5,7,10-tetramethyl-1,6-
diazacyclodecane (81). This compound was formed by the reduction of
the intermediate dioxy derivative (80) which resulted from the conden-
sation of the hydroxylamine (79) with acetonylacetone; the latter is
present on account of the partial hydrolysis of the dioxime in acidic

medium.

Reductive cyclization of trans-o-nitrostilbene (82) with
triethylphosphite yielded 2-phenylindole (84) and traces of two other
products. When this reaction was interrupted after one hour, the
intermediate 1-hydroxy-2-phenylindole (83) was isolated, but only in
poor yield (Sundberg, 1965).
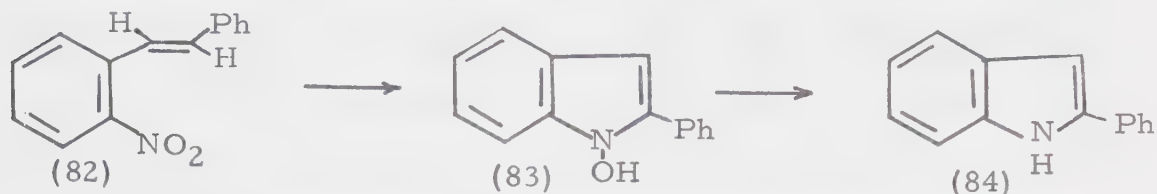
The tautomeric N-hydroxyquinolone (86, R=H) was pre-
pared by the stannous chloride/hydrogen iodide reduction of ethyl
o-nitrobenzoylacetone (85, R=H)   (Gabriel and Gerhard, 1921).   The
related compound (86, R=COOEt) was obtained by the reduction of
ethyl o-nitrobenzoylacetoacetate (85, R=COOEt) with stannous chloride
and hydrochloric acid in acetic acid (McCluskey, 1922).
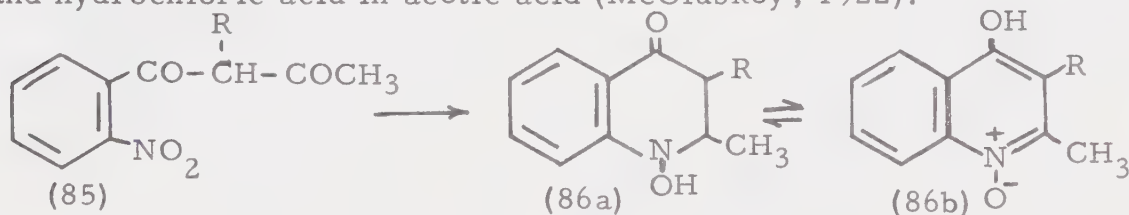
Reduction of o-nitroanilides (87) under mild conditions
resulted in the formation of 1-hydroxybenzimidazoles (89).   The
hydroxylamine (88) was postulated as an intermediate.   Among the
reducing systems used in this type of reaction are zinc and ammonium
chloride (Niementowski, 1910; Kuhn and Blau, 1958), zinc and hydro-
chloric acid (Niementowski, 1892, 1899), tin and hydrochloric acid
(Baczynski and Niementowski, 1902); ammonium sulfide (Bankiewicz,
1889; Niementowski, 1910; Takahashi and Kano, 1964), sodium
dithionite (Fries and Reity, 1937; De Stevens et al, 1967) and

catalytic hydrogenation over palladium (Kamel et al, 1957).

(87) (88) (89)
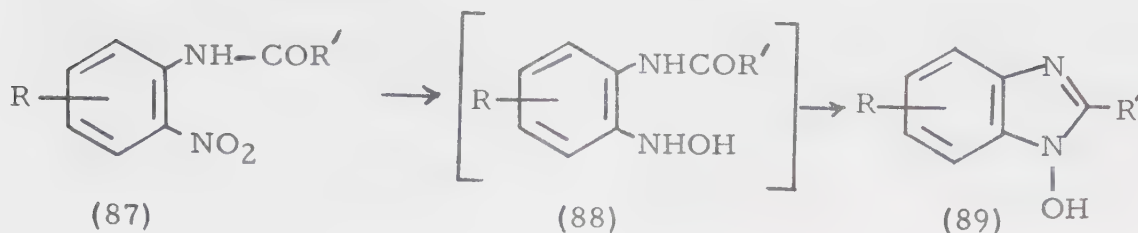
Ammonia (Neadle and Pollitt, 1967) as well as sodium hydroxide
(De Stevens et al, 1967) were also used to catalyze this cyclization.

The 1-hydroxybenzotriazole derivative (92) has been
prepared either by the stannous chloride/hydrochloric acid reduction
of the potassium salt of the 2-nitrosoimino oxime (90) (Harden and
Okell, 1901) or by the interaction of 1,2-naphthoquinone 1-oxime (91)
and toluene p-sulfonhydrazide (Scott and Lelor, 1966).

(90) (91) (92)
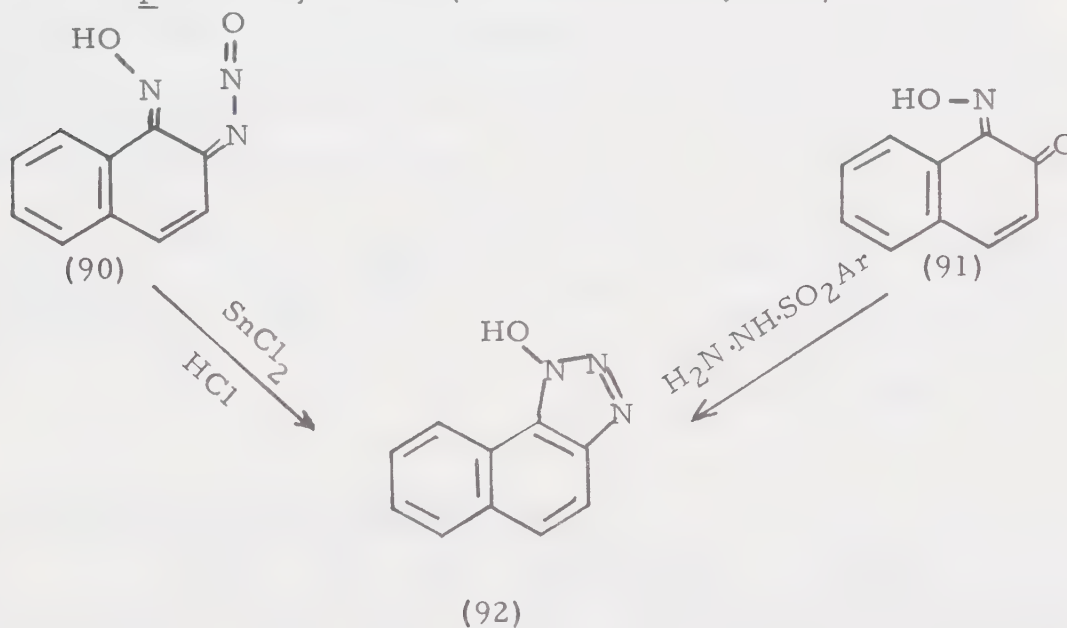
An early report (Heller and Wunderlich, 1914) that
reduction of ∝-cyano-o-nitrocinnamide (93) by zinc and acetic acid
yielded 2-carbonyl-2-cyanodihydroindole (94) and its N-hydroxy
derivative (95) was later discounted. The products have been
reformulated as 2-aminoquinoline-3-carboxamide (96) and its N-oxide
(97)(Pachter and Kloetzel, 1951; Taylor and Kalenda, 1953;

(93) (94) (95) (96) (97)
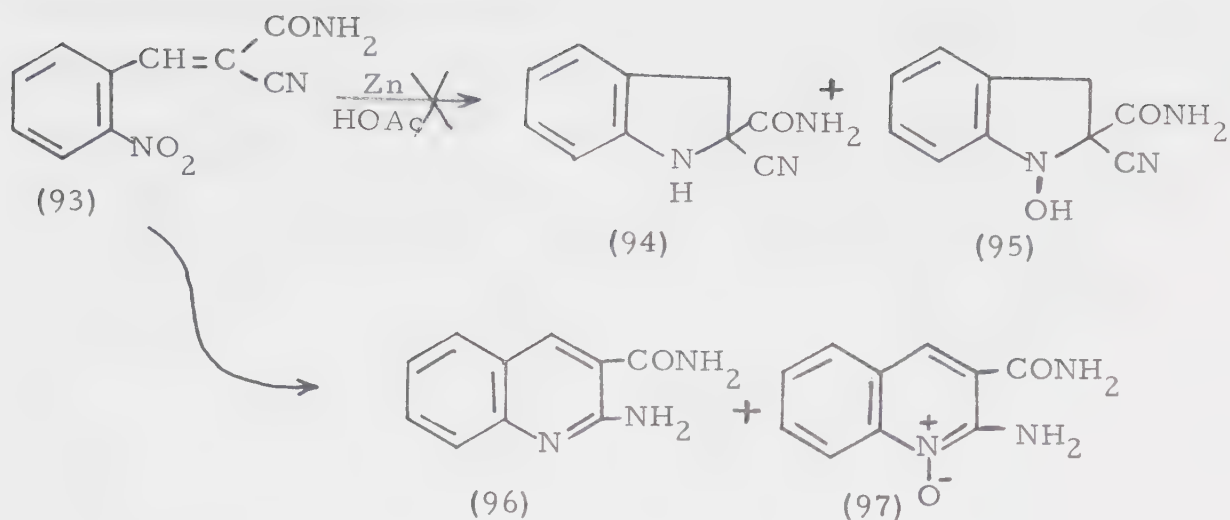
Tyler, 1955).

Another report by Narang et al (1934) and the related work by Coutts and Edwards (1966) regarding the formation of the N-hydroxy-pyrazoloquinolines (99) by the reduction of the o-nitrobenzylidene derivatives (98) constitutes a part of the present investigation and will be discussed in detail later.

(98) (99)
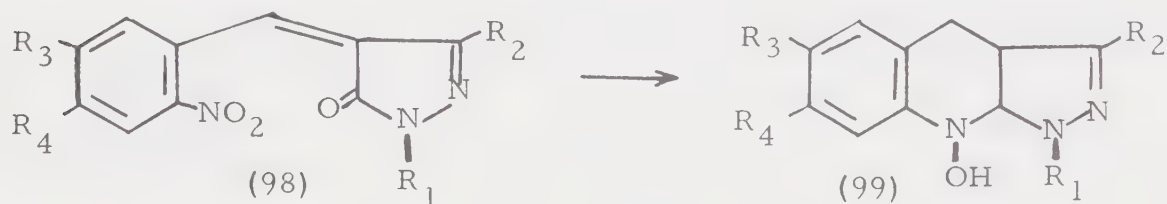
ii - Non-reductive cyclization:

In most cases, these cyclizations are catalyzed by acids or bases and the products occasionally are affected by the pH of the reaction media. Some interactions, however, occur under seemingly neutral conditions.

One of the earliest examples of acid-catalyzed cyclizations was that reported by Fischer and Hutz (1895). Treatment of the benzoin oxime (100) with concentrated sulfuric acid resulted in the formation of 1-hydroxy-2-phenylindole (83). A similar procedure

was recently employed for the preparation of some related N-hydroxy-indoles (Kawana et al, 1965).

(100)   (83)
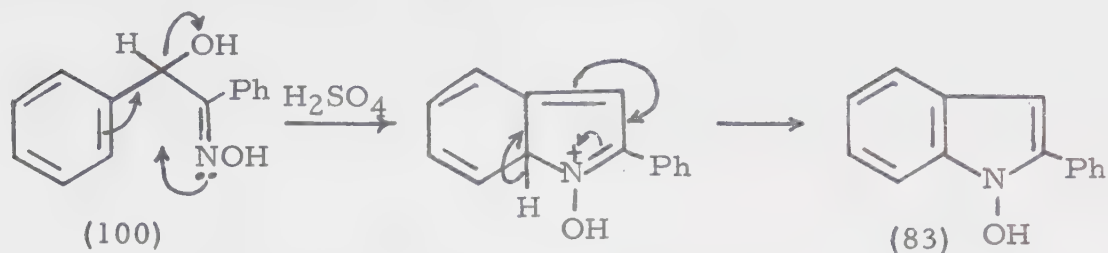
The related 3-cyano-1-hydroxy-2-phenylindole (103) was obtained by the action of potassium cyanide on either o nitro-α-phenyl-cinnamonitrile (101) or α-o-nitrophenylcinnamonitrile (102). Alkaline hydrolysis and decarboxylation of (103) yielded 1-hydroxy-2-phenyl-indole (83) (Loudon and Tennant, 1960).

(101)

(102)

(103)
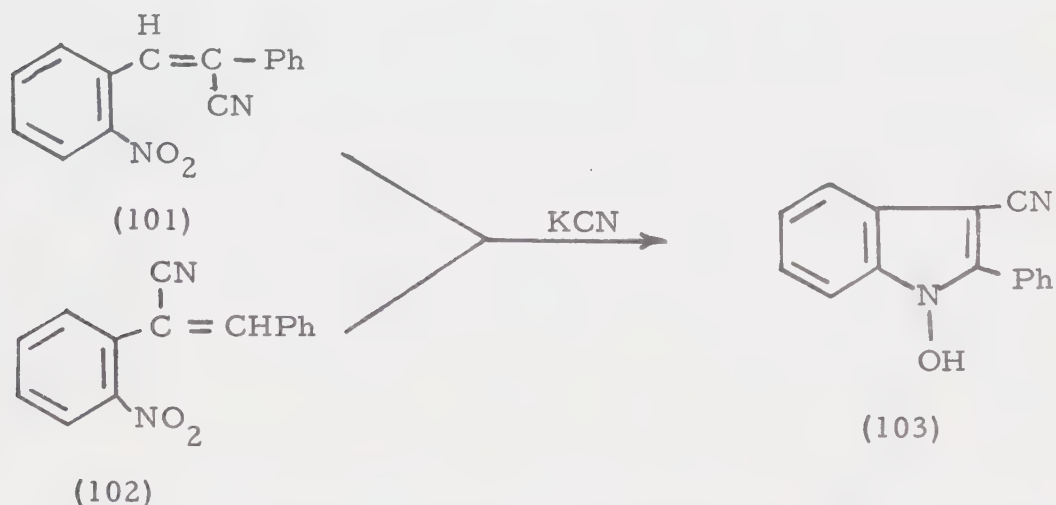
The acid-catalyzed condensation of o-nitrobenzaldehyde (104) with ethylacetoacetate (105) gave a 1-hydroxyquinolone derivative (106) (Loudon and Wellings, 1960). Analogous results were obtained by replacing the ketoester (105) with acetylacetone, benzoylacetone or diethylacetone dicarboxylate. When hydrogen chloride was used to catalyze the reaction, a chlorine atom was introduced into the product (106, X=Cl). However, no brominated derivatives were formed when hydrogen bromide was used. In the presence of quinol, the isolable

intermediate (107) may be cyclized even by hydrogen chloride without any uptake of chlorine (Loudon and Tennant, 1962).

(104) (105) (106)

(107)
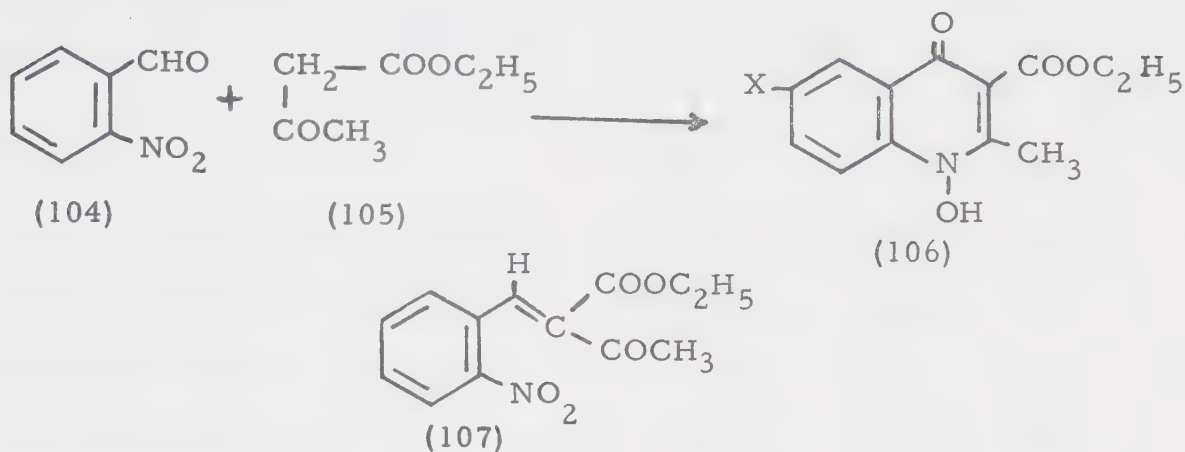
o-Nitrobenzaldehyde (104) reacted with benzene in the presence of sulfuric acid to give 10-hydroxyacridone (108) (Lehmstadt, 1932; Kliegl and Brosamle,1936). The anthranil oxide (109) and the nitroso compound (110) were suggested as intermediates (Katritzky and Logowski, 1971).

(104) H₂SO₄ (108a)

(109) (110) (108b)
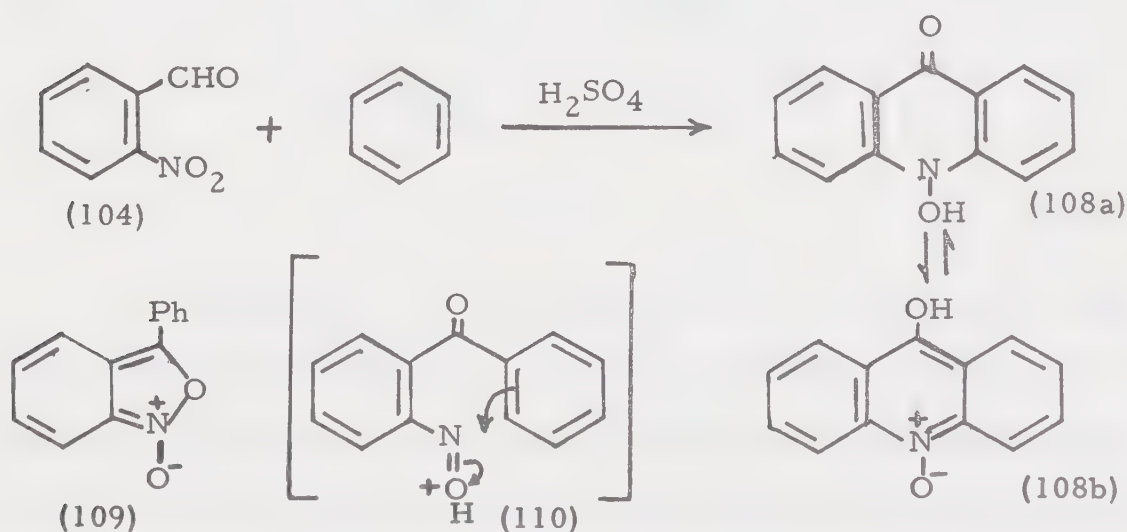
Nitrosation of 3-methyl-4-phenyl-3-buten-2-one oxime (111) yielded a high melting product which was initially assigned a nitrimine structure (Harris and Tietz, 1904) but was subsequently shown by Freeman and Gannon (1966) to be the 1-hydroxypyrazole 2-oxide (112a) or its 2-hydroxy 1-oxide tautomer (112b). Further

studies (Freeman and Gannon, 1969; Freeman et al, 1969) showed

$$CH_3-C \!\!=\!\! C-CH_3 \quad \xrightarrow[\text{HOAc}]{HNO_2}$$
$$\quad | \quad\quad | $$
$$Ph-CH \quad NOH$$

(111) (112a) ⇌ (112b)
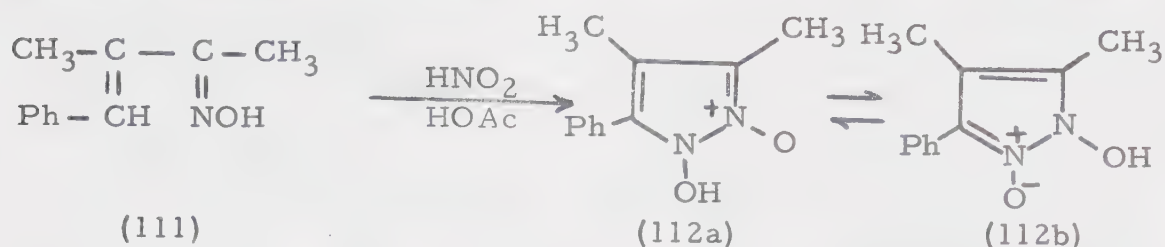
that the products obtained from this reaction are dependent on the

substituents on the oxime molecule. An attempt to prepare the

N-hydroxy N-oxide (114) by nitrosation of benzalacetophenone oxime

(113) resulted instead in the formation of a dimeric product (115)

(Freeman and Hansen, 1972).

$$PhCH = CH-C-Ph \quad \xrightarrow[\text{CH}_3\text{OH}]{C_5H_{11}ONO}$$
$$\quad\quad\quad\quad ||$$
$$\quad\quad\quad\quad NOH$$

(113) (114)

(115)
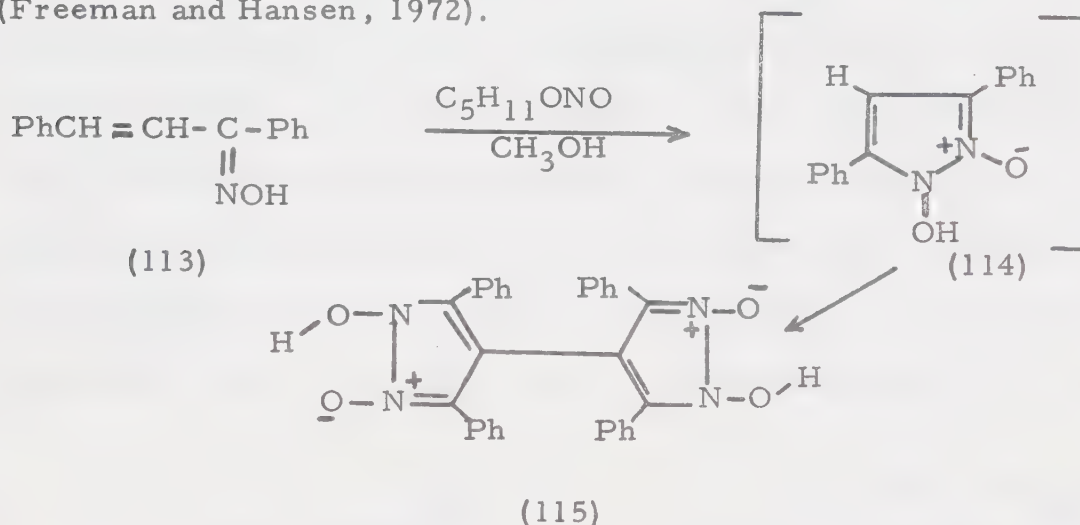
The ability to form cyclic N-hydroxy compounds by base-

catalyzed cyclizations has been known for some time. Reissart (1896)

found that treatment of o-nitrobenzylmalonic acid (116) with aqueous

sodium hydroxide solution yielded 1-hydroxyindole-2-carboxylic acid

(77). This compound was also obtained by the action of the same

base on o-nitrobenzylacetoacetate (117) (Gabriel et al, 1923). The

latter reaction occurred so readily that the ester (77, $COOC_2H_5$ for

COOH) was also isolated.

(116)

(117)

NaOH →

(77)
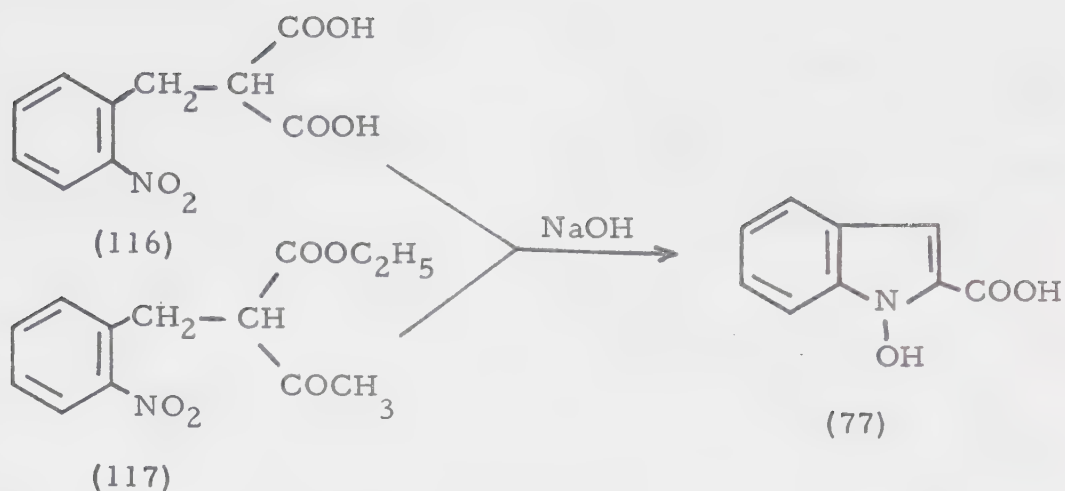
Base-catalyzed cyclizations of diethyl- α-cyano- α-2-nitro-benzylmalonate (118) and its α-carbamoyl analog (121) produced different products depending on the type of base used. Thus, treatment of (118) with ethanolic potassium hydroxide yielded the 1-hydroxyquinolone (119) while the use of aqueous sodium carbonate led to the formation of ethyl 3-cyano-1-hydroxyindole-2-carboxylate (120). On the other hand, treatment of the α-carbonylmalonate (121) with

(118)

KOH / EtOH →

Na₂CO₃ →

(119)

(120)
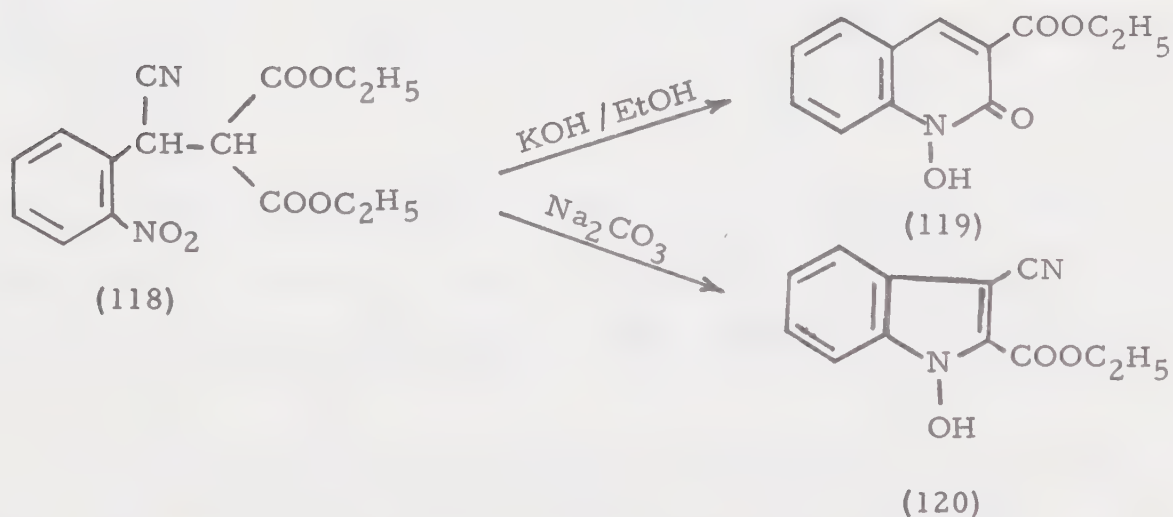
aqueous sodium hydroxide gave the acid amide (123) while the corresponding ester (122) was obtained when sodium carbonate was used (Loudon and Wellings, 1960). These cyclizations have been explained

(121)
(122)
(123)
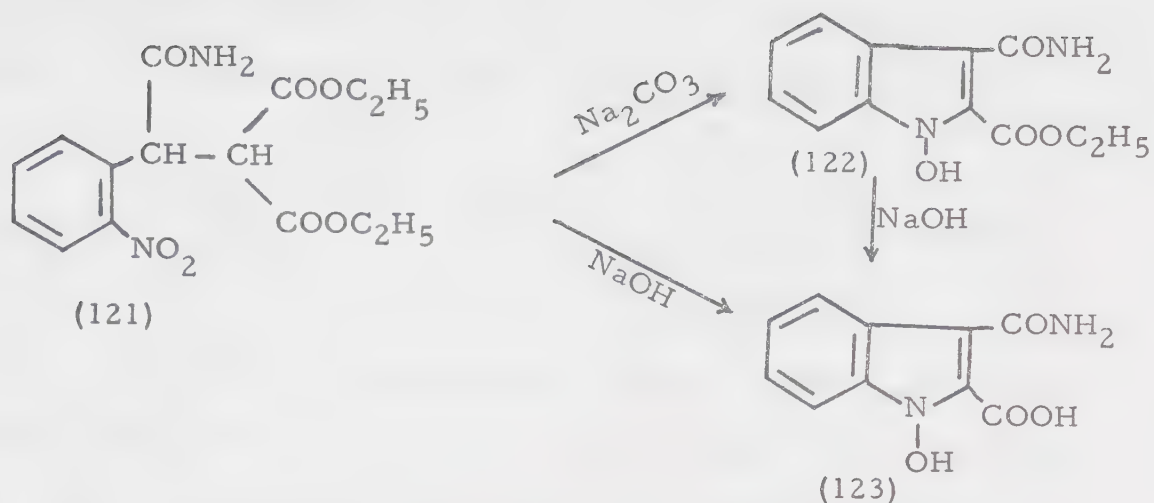
in terms of intramolecular condensation reactions of carbanions with the nitro groups followed by decomposition of the internal condensate (124) (Loudon and Wellings, 1960).

(124)
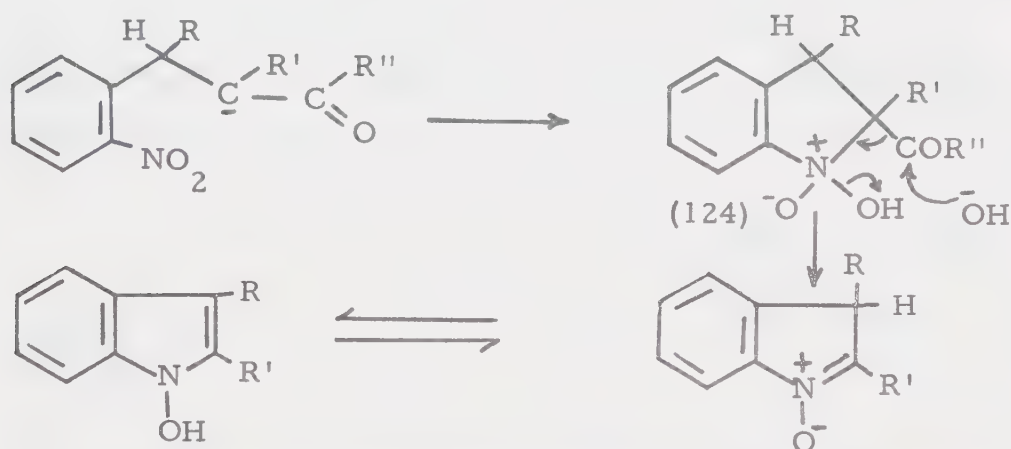
2-Nitro-N-phenacyl-$\underline{p}$-toluidine (125) was found to cyclize in the presence of ethanolic potassium hydroxide to the 1-hydroxy-imidazole (126) (Loudon and Tennant, 1963). The analogous 1-hydroxy-

(125)
(126)
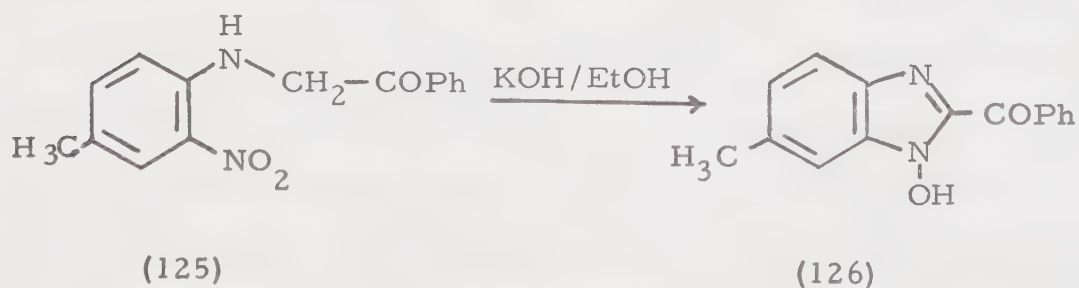
2-methoxycarbonyl-6-nitrobenzimidazole (128) was obtained by the

base-catalyzed cyclization of methyl α-(2,4-dinitrophenylamino)-

acrylate (127) (Luetzov et al, 1966; Luetzov and Vercellotti, 1967).

(127) → OH⁻ → (128)
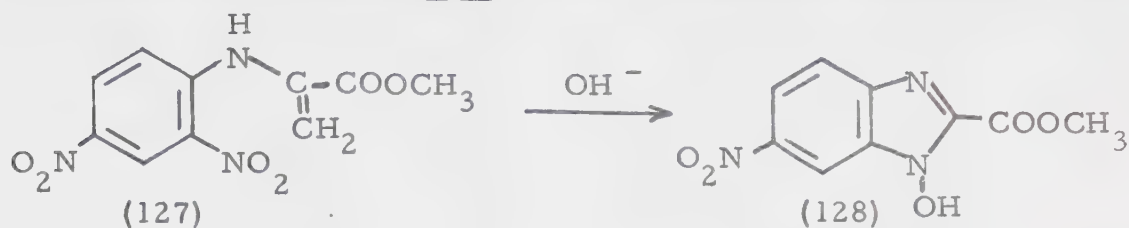
1-Hydroxy-2-phenylbenzimidazole (130) was prepared by

the base-catalyzed cyclization of N-benzyl-o-nitroaniline (129) (Stacy

et al, 1966).   The same compound was also obtained by the reaction of

(129) → OH⁻ → (130)
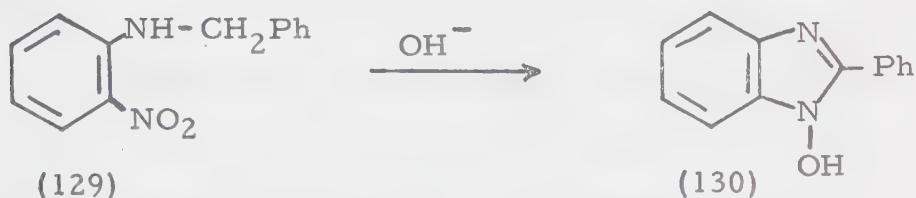
benzaldehyde and o-nitroaniline (131) and by the prolonged heating of

the isolable intermediate benzal-o-nitroaniline (132) (Stacy et al, 1964).

(131) + PhCHO → (132) → (130)

The analogous 1-hydroxybenzimidazole derivative (134)

were prepared by the photolytic conversion of 2,4-dinitrophenyl

derivative of α-amino-acids (133).   This reaction also produced

4-nitro-2-nitrosoaniline (135).   The proportion of these two products

depends on the pH of the solution (Pollitt, 1965; Neadle and Pollitt,

1967).   Reaction of (135) with different aldehydes yields 1-hydroxy-6-

nitrobenzimidazoles (134) (Russel, 1965).
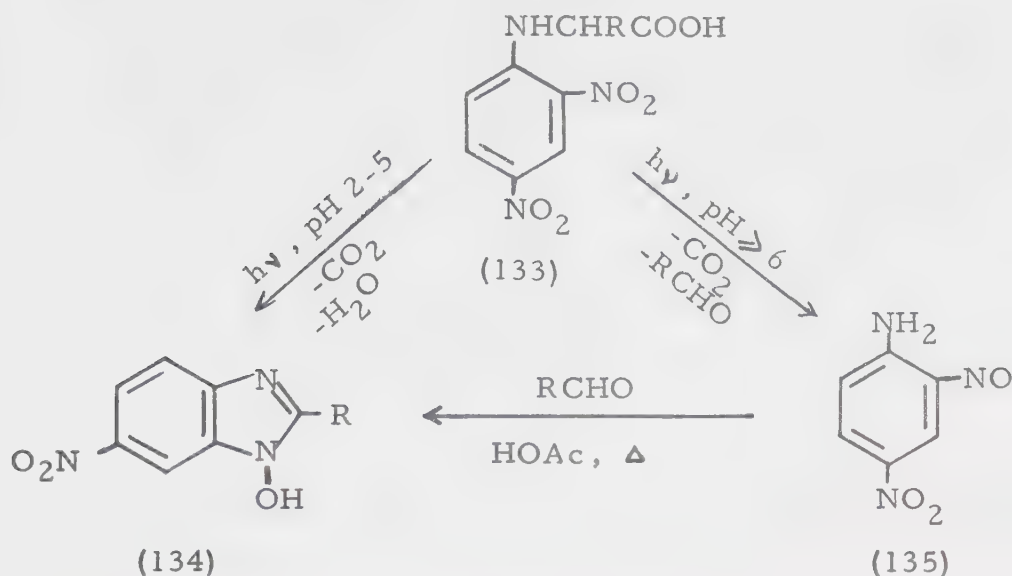
Treatment of 1,3-dimethyl-4-amino-5-nitrosouracil (136) with benzaldehyde and dimethylformamide yielded the tautomeric N-hydroxypurine (138) as one of the reaction products. This compound is probably formed by the spontaneous cyclization of the intermediate anil (137) (Taylor and Garcia, 1964).
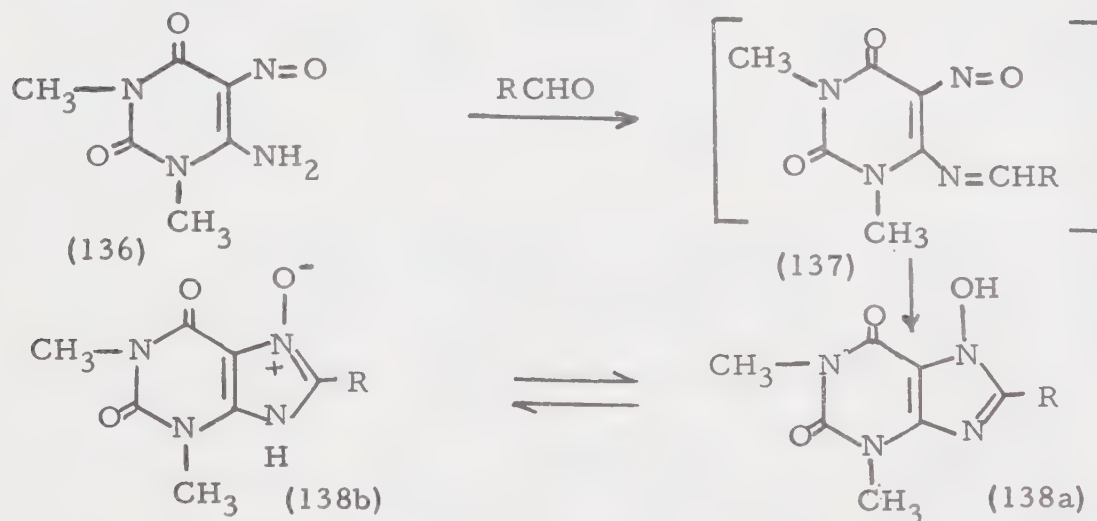
1-Hydroxy-2-phenylbenzimidazole 3-oxide (142) was obtained by the interaction of nitrosobenzene (139) with benzonitrile oxide (140). The intermediate (141) has been isolated at low temperature (Minisci et al, 1963). Related compounds have also been prepared
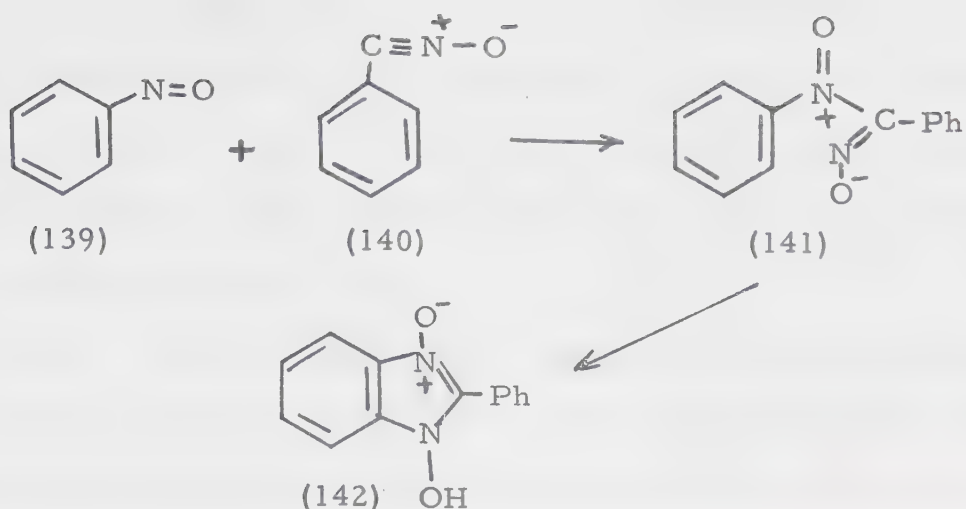
by the reaction of o-quinone dioxime with aldehydes (Boulton et al, 1966, 1967).

The 1-hydroxyindazolone derivatives (144a) which are tautomeric with 3-hydroxy-indazole-1-oxide (144b) were reported to be formed by the isomerization of (2-nitrobenzylidene)anilines (143) in the presence of sodium bicarbonate (Secareanu and Lupas, 1933).
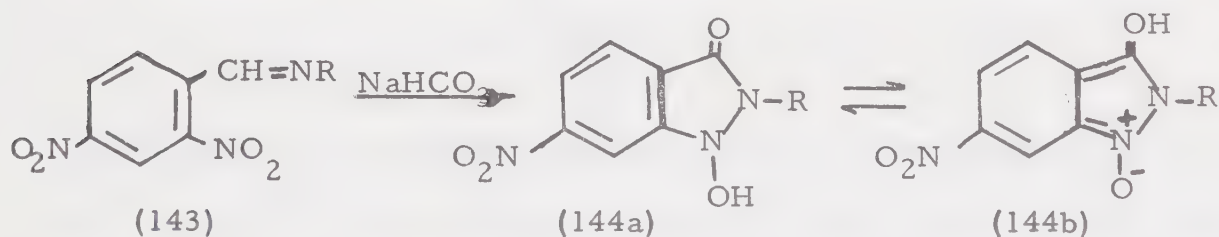
1-Hydroxybenzotriazole (146) was the product of a base-catalyzed cyclization of o-nitrophenylhydrazine (145) (Nietzki and Braunschweig, 1894; Zincke and Schwarz, 1900). This reaction was
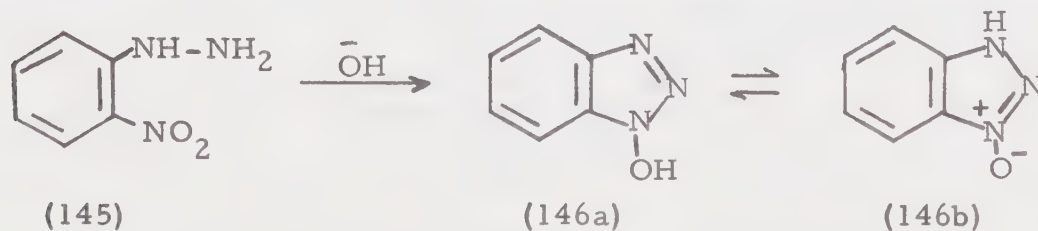
extended to the preparation of 1-hydroxy-6-nitrobenzotriazole by the action of hydrazine hydrate on 2,4-dinitrophenylhydrazine (Curtius

and Mayer, 1907). The reaction of hydrazine hydrate with o-halogeno-nitrobenzenes (Muller and Zimmermann, 1925) or with o-dinitro-benzenes (Vis, 1939) also gave rise to 1-hydroxybenzotriazoles. Yields varied greatly according to the pH of the reaction media (Macbeth and Price, 1934).

Some monocyclic N-hydroxy compounds can also be prepared by cyclization reactions. The 1-hydroxypyrroles (149) were formed by the condensation of benzil oximes (147) and vinyltriphenyl-phosphonium bromide (148) in a reaction designed for the preparation of 6H-oxazines (150) (Schweizer and Kopay, 1972). Other substituted
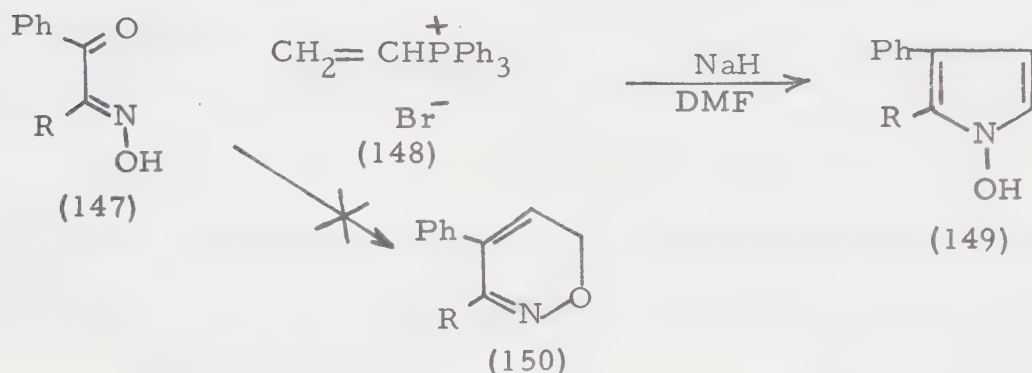
N-hydroxypyrrole derivatives (153) are the products of the reaction of the oxime (151) with various diketones (152) (Spiro and Vaccaro, 1959).
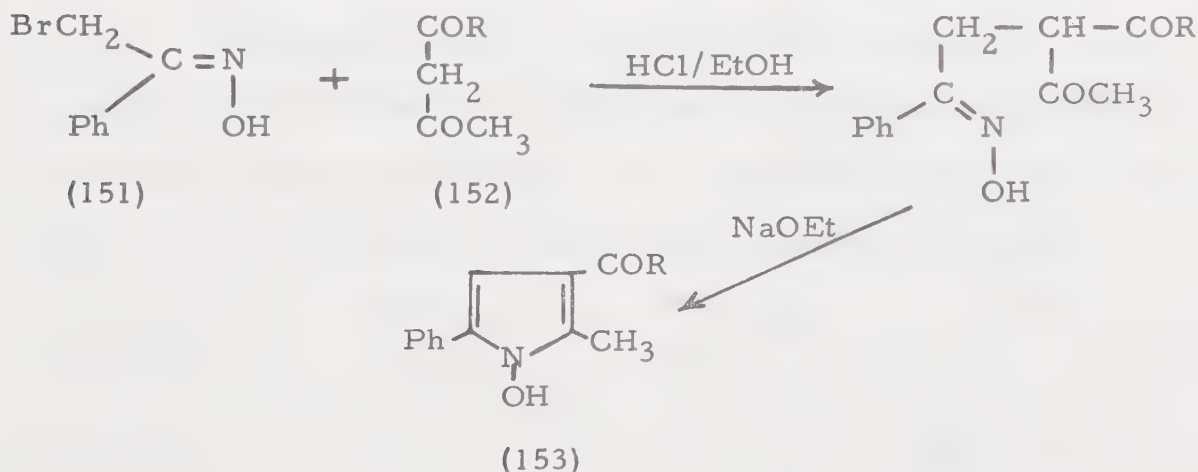
The cyclization of 2,6-dimethylheptadiene-4-one (154) with hydroxylamine offered a means of preparing the 1-hydroxy-4-piperidone

derivative (155) (Lehmann, 1897).

(154) → (155)
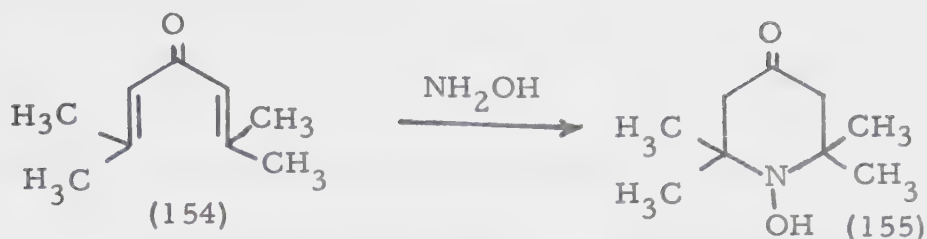
N-Hydroxyimidazoles (157) are formed by the reaction of α-ketoxime (156) with aldehydes in the presence of ammonia (Allan and Allan, 1964; Akagane et al, 1969). This reaction was originally discovered by Diels (1918) but the products were allocated inaccurate structures (Diels and Solomon, 1919). An alternative preparation of

(156) + R'CHO → (157)
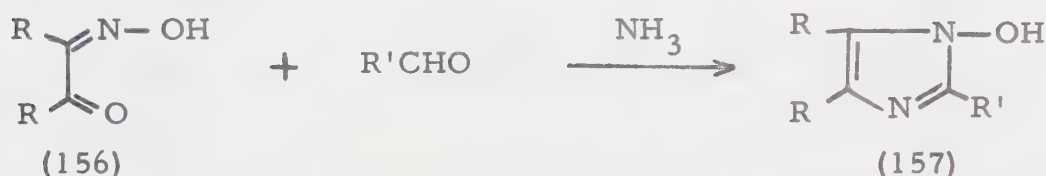
this type of compound was achieved by reacting aldehydes with amino-oximes (158) (Busch, 1931; Busch and Kammerer, 1930).

(158) → (159)
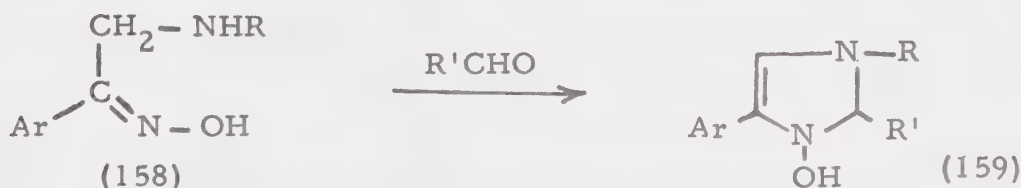
Condensation of 2,3-butanedione mono-oxime (160) with aldoximes (161) resulted in the formation of substituted 1-hydroxy-imidazole-3-oxides (162) (Wright, 1964; Bodendoff and Towliati, 1965). Similar products have been obtained by the reaction of dimethyl-

(160) + (161) → (162a) ⇌ (162b)

$$H_3C-C=NOH$$
$$H_3C-C=NOH$$

(163)
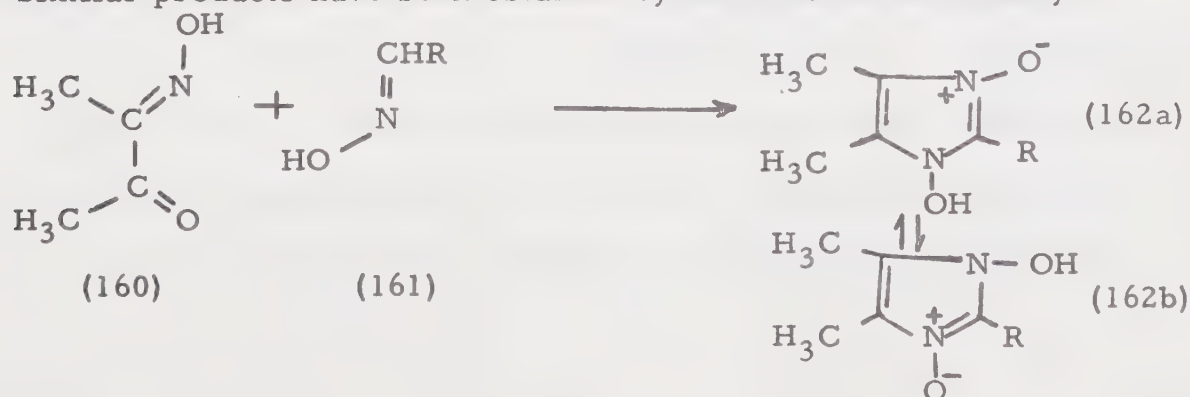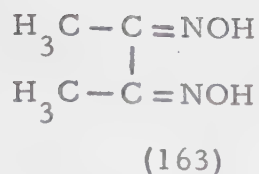
glyoxime (163) with aldehydes (Laparola, 1945).

$\propto$-Hydroxylamino-oximes (164) when reacted with aldehydes yield dihydro-1-hydroxyimidazole 3-oxides (165). These compounds were readily converted to hydroxylamines (166) or (167) by acylation followed by heat or by the action of hydrogen chloride in ethanol (Volodarsky et al, 1965).
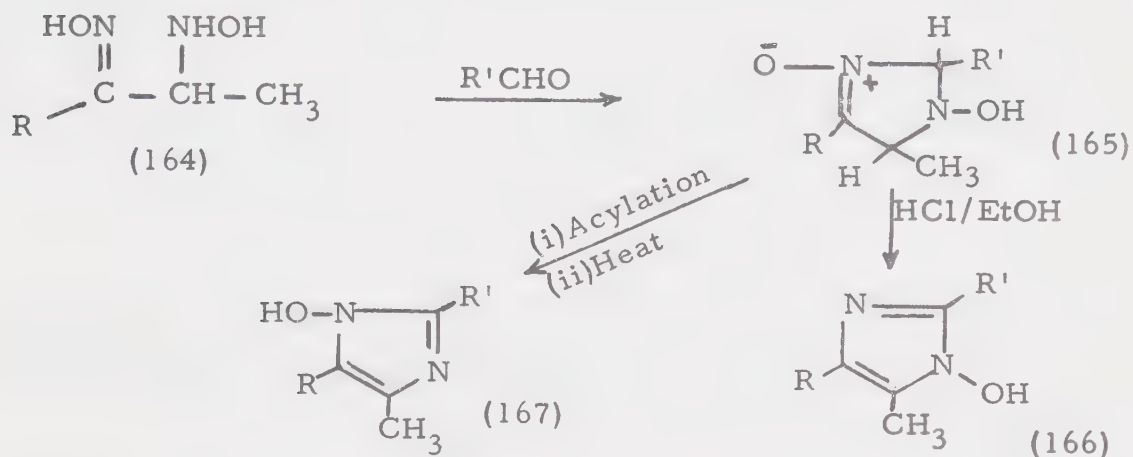
4-Hydroxy-1,2,4-triazoles (169) are produced by the reaction of hydroxylamine with dichloro compounds of general structure (168) (Stolle and Thöma, 1906). Also, addition of nitril-

imines (170) to the C=N double bond of aldoximes (171) produced 1-hydroxy-4-phenyltriazole (172) but these compounds dehydrated spontaneously to give 1,2,4-triazoles (173) (Huisgen et al, 1965).
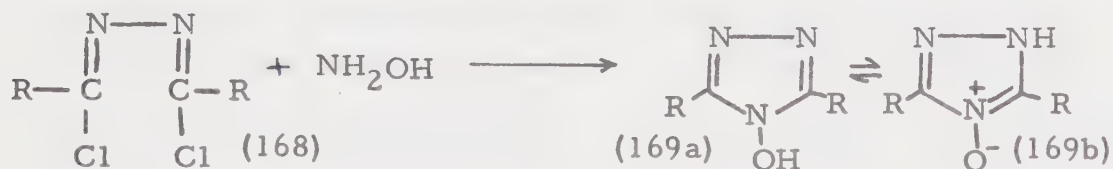
(170) (171) (172) (173)
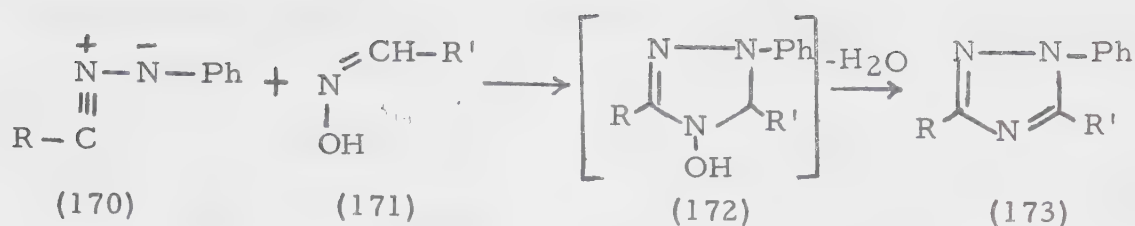
The reaction between hydroxamoyl chloride (174) and
sodium azide gave 1-hydroxy-2-phenyltetrazole(175) (Eloy, 1961).
The latter compound was also obtained by the action of nitrous acid
on hydroxamoyl hydrazine (176) (Wieland, 1909). Some related

(174)

(176) (177) (175)
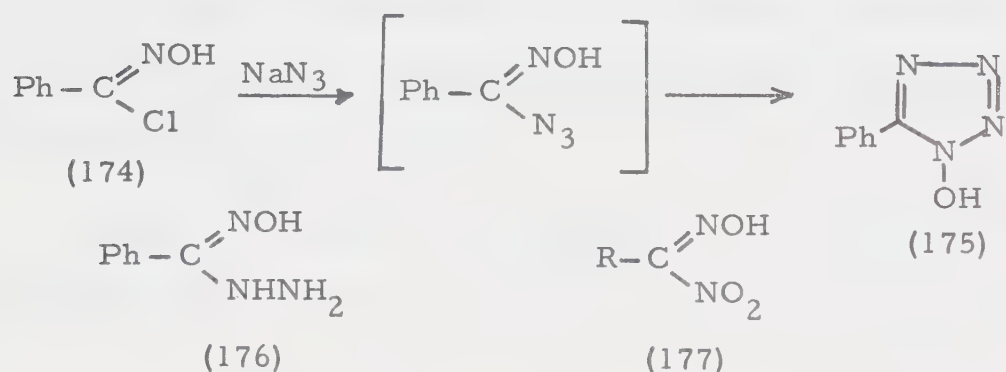
derivatives were prepared by the condensation of nitrolic acid (177)
with hydrazoic acid (Maffei and Bettinetti, 1956).

O-Alkyl and O-acyl derivatives of cyclic hydroxylamines
are formed by cyclization reactions. Thus, condensation of 1,4-
dibromobutane (178) with O-methylhydroxylamine (179) yielded 1-
methoxypyrrolidine (180). 1-Methoxypiperidine was similarly
prepared from 1,5-dibromopentane (Zinner and Moll, 1966).

(178) (179) (180)

N-Methoxyaziridines of the type (184) were obtained by
the reaction of methylnitronates (181) and acetylenes (182); N-methoxy-

4-isoxazolines (183) were postulated as intermediates (Tartakovskii et al, 1968).

(181)   (182)   (183)   (184)
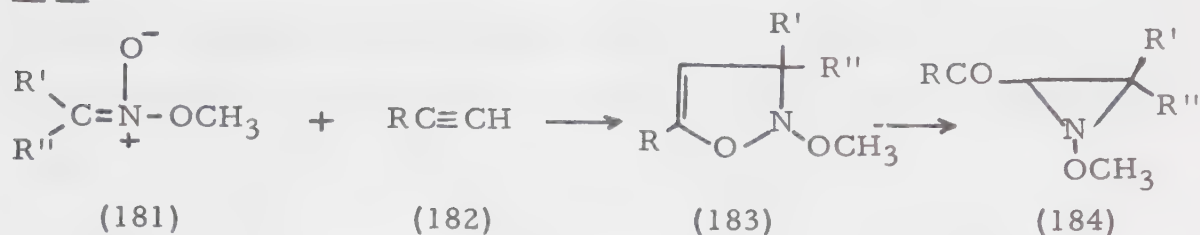
The N-alkoxy and N-aryloxytriazines (186) can be prepared by the reaction of the diguanid ethers (185) with carbonyl compounds in the presence of hydrochloric acid. Catalytic hydrogenation of (186) gave the parent N-hydroxydihydrotriazine (186, OH for OCH_2R) (Mamalis et al, 1962, 1965).

(185)   (186)
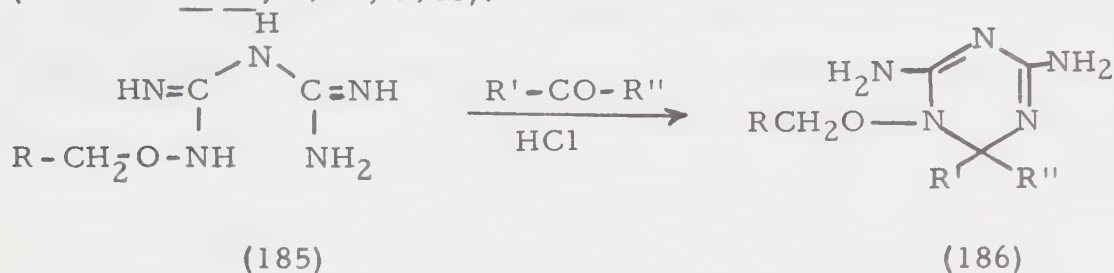
N-Benzoyloxy and N-sulfonyloxy derivatives of 2-aza-norbornenes (188) were formed by the addition of cyclopentadiene to various oxime benzoates or sulfonates (187) (Biehler and Fleury, 1968).

(187)   (188)
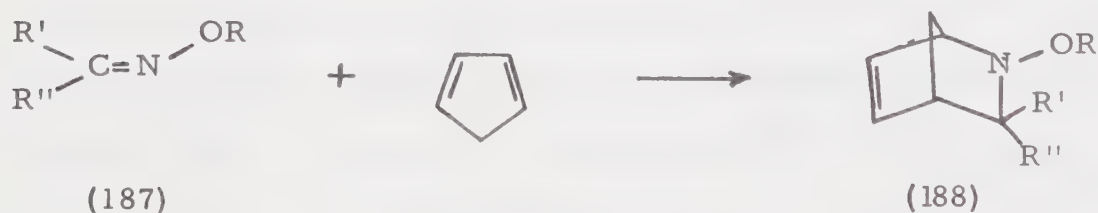
(E)   Miscellaneous Preparations:

Included under this heading are those preparations which do not fit into any of the preceding classifications.

Certain types of amine oxides such as (189) decompose when heated to yield a hydroxylamine plus an olefin. Examples of

this reaction are reported in the early literature (Wernick and Wolffenstein, 1898; Mamlock and Wolffenstein, 1900). An intra-molecular mechanism involving a planar, five-membered cyclic transition state was suggested for this reaction (Cope and Trumbull, 1960).

(189)
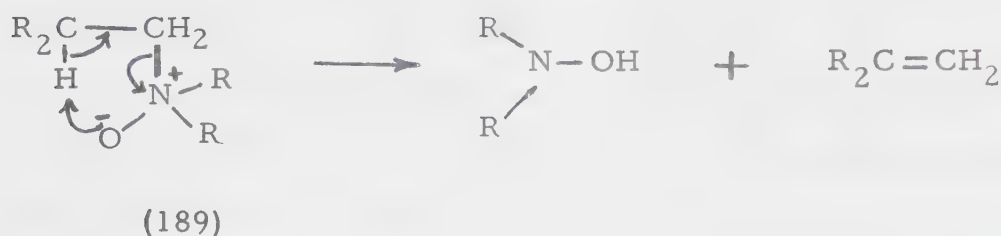
The early report (Wernick and Wolffenstein, 1898) that N-hydroxypiperidine (23) was obtained by pyrolysis of N-ethylpiperidine oxide (190) was confirmed by Rogers (1955) who extended this

(190)   (23)
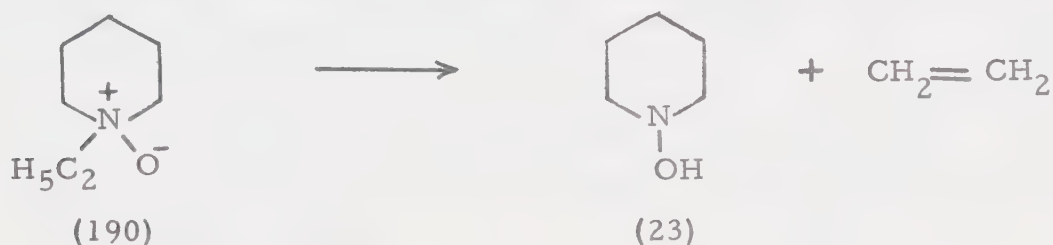
work to the preparation of other N-hydroxy compounds. For example, 1-hydroxymorpholine (22) was obtained by heating the phthalate salt of ethyl β-morpholinopropionate N-oxide (192) with aqueous ammonia. This N-oxide was prepared by the action of monoperphthalic acid on the ester (191). Similarly, 1-hydroxypiperidine (23) was formed

(191)   (192)   (22)
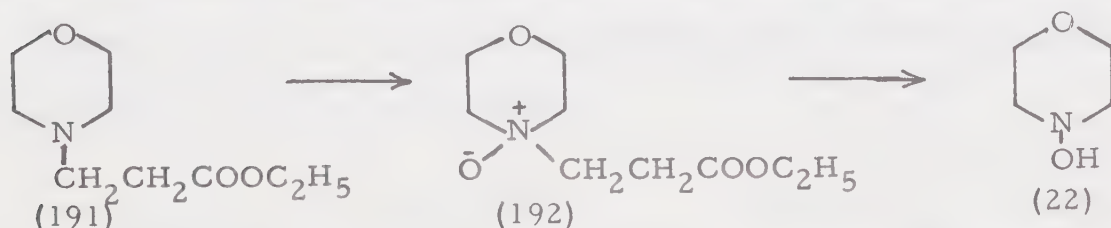
when ethyl β-piperidinepropionate was treated with perbenzoic acid; in this case, the N-oxide benzoate was not separated. Both these reactions, which were carried out under mild conditions, have been

described as a reversal of the Michael addition, facilitated by the formal positive charge on nitrogen (Rogers, 1955).

1-Hydroxypyrrolidine (4) and 2-hydroxy-1,2,3,4-tetra-hydroisoquinoline (193) were similarly prepared by the pyrolysis of N-ethylpyrrolidine N-oxide (Thesing and Sirrenberg, 1959) and N-(carbethoxyethyl-1,2,3,4-tetrahydroisoquinoline) N-oxide (Thesing and Mayer, 1957) respectively. Compound (4) was also obtained by the pyrolytic decomposition of the N-oxide (194) under reduced pressure (Paquette, 1962).

(4)

(193)

(194)
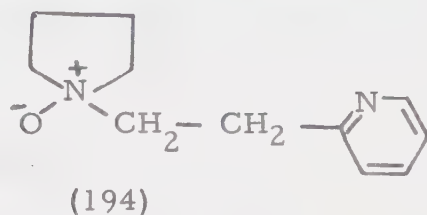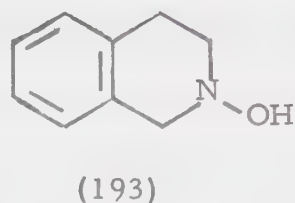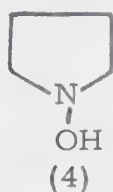
Some cyclic hydroxylamines are prepared by chemical modification of compounds which already have the N-hydroxy function. For example, lithium aluminum hydride reduction of N-hydroxy-succinimide (195a) and its O-methyl analog (195b) yielded the corres-ponding derivatives of pyrrolidine (196) (Zinner and Moll, 1966). Similar reduction of 3-hydroxyphthalimide gave N-hydroxyisoindoline (197) (Zinner and Dueerkop, 1969).

(195)   (196)   (197)
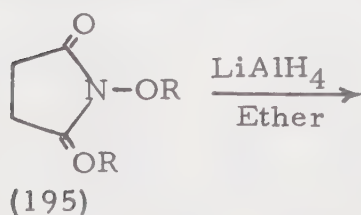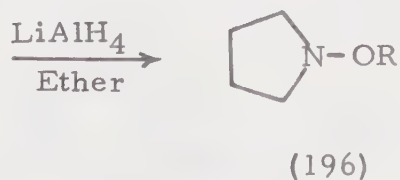
a, R = H   b, R = CH$_3$
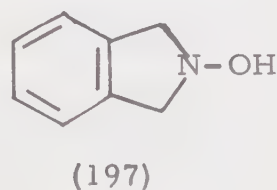
Also, mild reduction of 1-hydroxypyrazole 2-oxides (198) with sodium dithionite yielded 1-hydroxypyrazoles (199); zinc and acetic acid reduced both the N-oxy and N-hydroxy functions (Freeman

(198)   Na$_2$S$_2$O$_4$ (199)
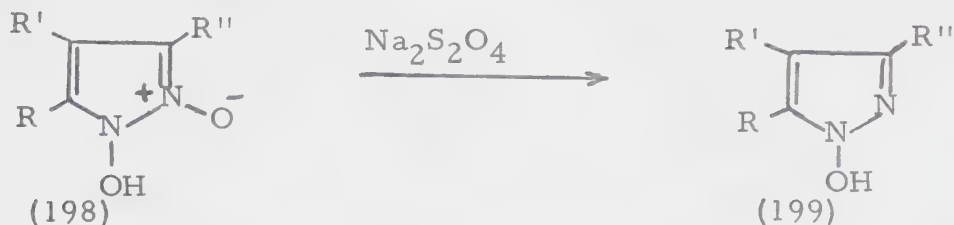
and Gannon, 1969). Similarly, cautious reduction of the dioxy derivative (142) with stannous chloride and hydrochloric acid resulted in the formation of 1-hydroxy-2-phenylbenzimidazole (130) (Minsci et al, 1963). The latter N-hydroxy compound was said to be formed by the action of alkaline hydrogen peroxide on 2-phenylquinoxaline 4-oxide (200) (Hayashi and Iijima, 1962).

(142)   (130)   (200)
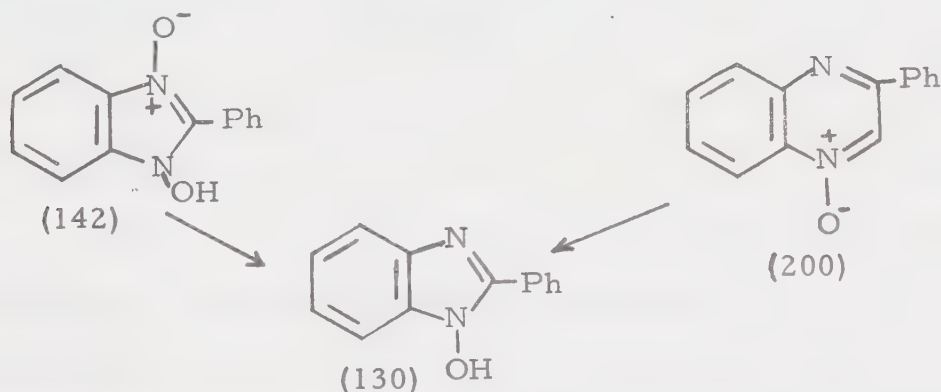
Reduction of the stable free radical (201) with phenyl-hydrazine or with hydrogen over platinum yielded 2,2,4,4-tetra-methyl-1,2,3,4-tetrahydro-3-hydroxy-γ-carboline (202). The radical (201) was obtained by the catalyzed (Na$_2$WO$_2$) hydrogen per-oxide oxidation of the γ-carboline (202, H for OH) (Rozantsev and Shapiro, 1964).

(201)   (202)
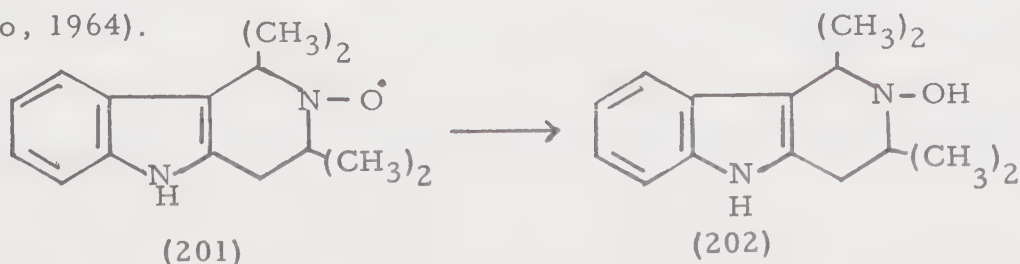
The reaction of ethanol with the pentafluoro compound (203) causes elimination of one molecule of hydrogen fluoride and the formation of 1-ethoxyaza-2-cycloperfluorobutene (204) (Knunyants and Bykhovskaya, 1960).

F_2C—NF
| |
$F C$=$C F$
(203)

EtOH
$\xrightarrow{\quad\quad}$
-HF

F_2C —N^{OEt}
| |
FC=CF
(204)
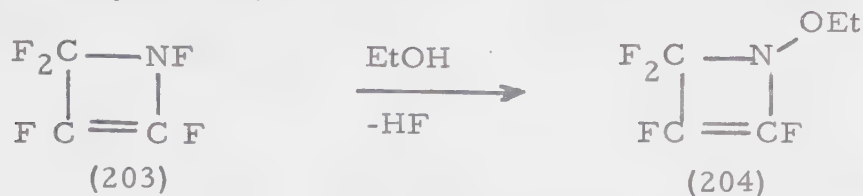
10-Hydroxyacridone (108) was prepared by acid hydrolysis of 9-bromoacridine 10-oxide (206) which in turn was obtained by the bromination of acridine-10-oxide (205) in acetic acid (Acheson et al, 1960).

(205) (206) (108)
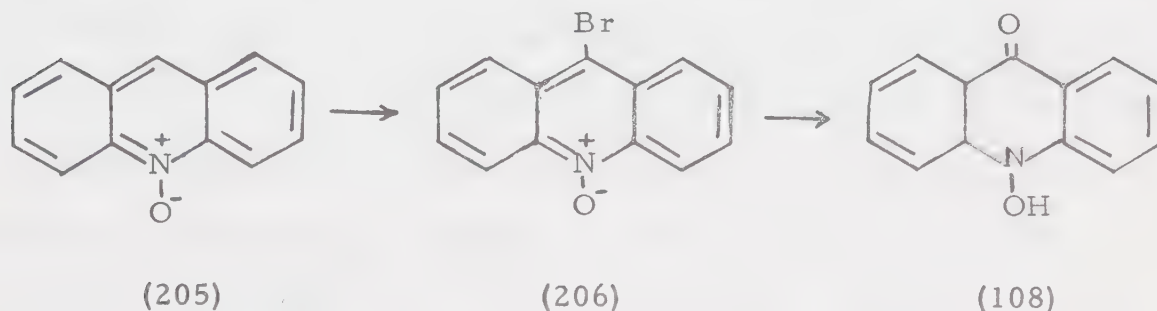
Heating the pyrazine N-oxide (207) with ethanolic hydrogen chloride offered the hydroxylamino-spirolactam (208). This compound is believed to be formed by the protonation of the N-oxide followed by intramolecular electrophilic substitution at the o-position

(207)

HCl/EtOH
$\xrightarrow{\quad\Delta\quad}$

(208)
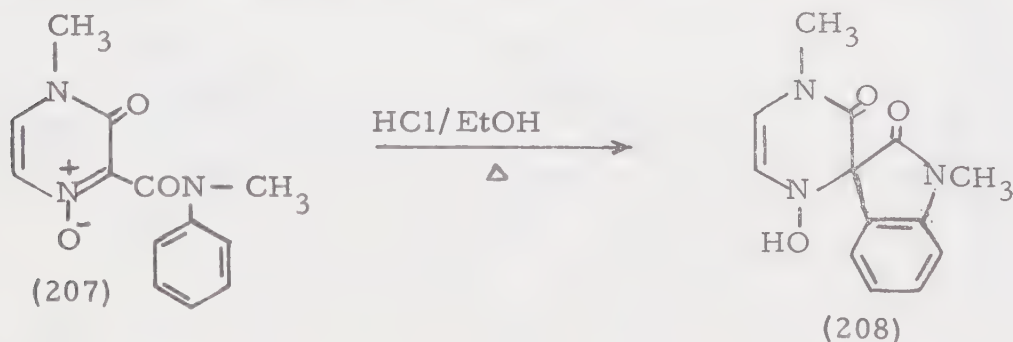
of methylanilide by the pyrazine 2-C-atom (Habib and Rees, 1962).

Alkylation of benzofuroxan (209) with the powerful alkylat-
ing agent, methyl trifluoromethane sulfonate resulted in the isolation
of the methylbenzimidazole (210) rather than the expected quaternary
salt.   A mechanism for this rearrangement was suggested by Boulton
et al (1966, 1967).

(209)   (210)
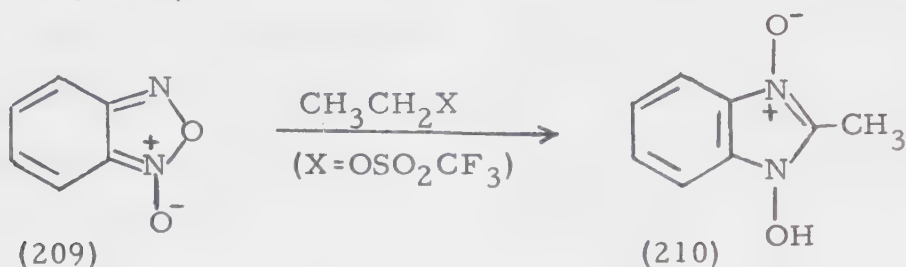
Condensation of 2,6-diphenyl-4-pyrone (211) with hydroxyl-
amine resulted in ring opening and then reclosure to give 1-hydroxy-
2,6-diphenyl-4-pyridone (212) and 4-hydroxylamino-2,6-diphenylpyridine
1-oxide (213).   The i.r. spectrum of (212) in chloroform showed that
it exists exclusively as the N-hydroxy form (212).   On the other
hand, the solid spectrum suggested a polymeric association (214)
(El-kholy et al, 1962).

(211)   (212)

(214)   (213)
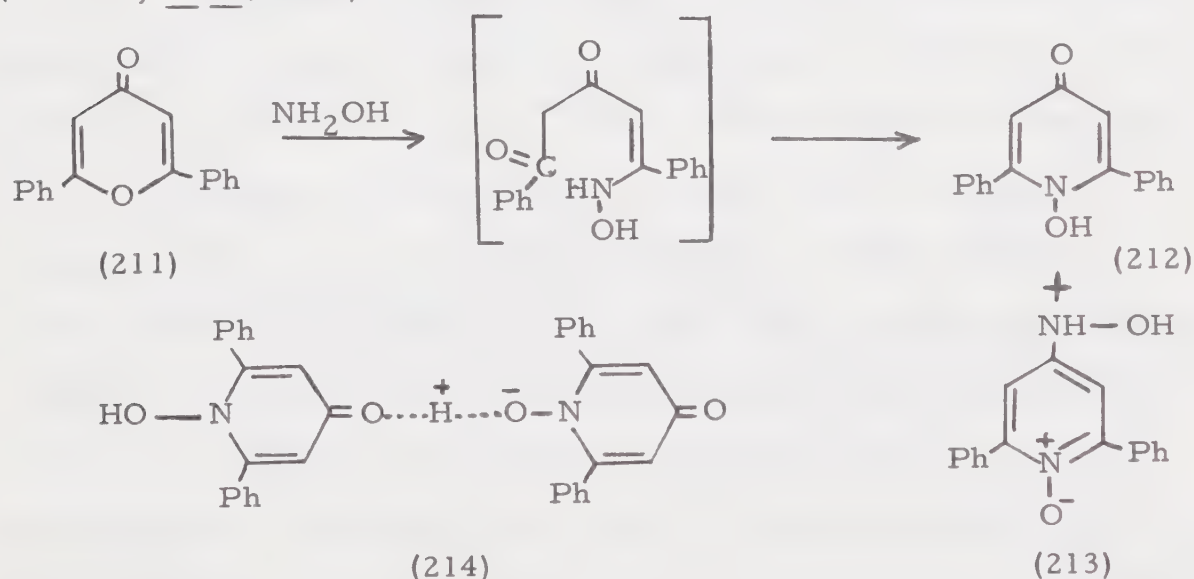
3. PHYSICAL AND CHEMICAL PROPERTIES OF CYCLIC HYDROXYLAMINES

The physical and chemical properties of cyclic hydroxyl-amines are related to those of their parent amines, but the presence of the N-hydroxy function also permits a number of reactions analogous to those found with arylhydroxylamines. There are also some similarities between the chemical reactivity of cyclic hydroxylamines and cyclic hydroxamic acids although the presence of a carbonyl function in the α-position of the latter may have profound effects on their solubility as well as on their chemical behavior. Also, in cases where the cyclic N-hydroxy compound exists in tautomeric equilibrium with the corresponding N-oxide, the properties demonstrated might be related to those of the N-oxides.

(A) Solubility and Salt Formation:

Solubility in water or organic solvents is influenced by the nature of the heterocyclic system incorporating the N-hydroxy function. However, solubility in alkalis or acids could be modified considerably by the introduction of this function. In many cases, N-hydroxy compounds are acidic and, therefore, soluble in alkali solutions. Stable sodium salts (Loudon and Tennant, 1960; Freeman and Gannon, 1969) as well as potassium, anilinium and hydrazinium salts (Curtius and Mayer, 1907) of some cyclic hydroxylamines have been prepared and identified. Insoluble copper salts of 1-hydroxyisoxazolidines (Kohler and Barrett, 1924, 1926) and insoluble silver salts of 1-hydroxy-benzotriazole (Brady and Day, 1923) are also known. The latter compounds have been used analytically for the determination of silver

(Singh and Kapil, 1960; Deorha and Soreen, 1964; Sharma and Mukerji, 1965). 1-Hydroxypyrazole 1-oxides form chelates with Cu^{+2}, Co^{+2}, Cd^{+2} and Ni^{+2} (Freeman and Gannon, 1969).

Some cyclic N-hydroxy compounds are basic enough to form acidic salts. For example, 1-hydroxypiperidine and 1-hydroxy-morpholine were isolated as hydrochlorides, picrates and acid oxalates (Rogers, 1956; Zinner and Kliegel, 1966). The third group of cyclic hydroxylamines contains compounds which are virtually neutral and form no salts. Examples are 1-hydroxy-2-phenylpiperi-dine (Kato and Yamanaka, 1965) and 1-hydroxy-2-methylindole (Acheson et al, 1970). Minor changes in structure sometimes alter the acidity and the solubility characteristics of N-hydroxy compounds. For example, 1-hydroxyimidazole (215, R=Ph) is amphoteric (pK_a 9.41, pK_b 9.36) while other 1-hydroxyimidazoles such as (215, R=CH_3) are not (Akagane et al, 1969).
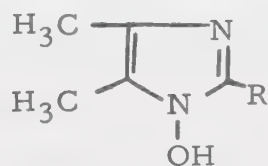
(215)

(B) Qualitative and Quantitative Determination:

Cyclic hydroxylamines readily reduce Tollen's and Fehling's solutions (Jones and Major, 1927; Habib and Rees, 1962; Feigl, 1966). The former reagent is used as a spray for the detection of N-hydroxy compounds on thin-layer chromatographic plates (Beckett and Salami, 1972). Some cyclic hydroxylamines also give a positive test with Schiff reagent (Zinner, 1957). Some of these compounds form a red color when treated with ferric chloride but not as spontaneous as

that obtained by hydroxamic acids with the same reagent. In fact, this color results from the oxidation of cyclic hydroxylamines to the corresponding hydroxamic acids (Elsworth and Lamchen, 1966). N-hydroxyindoles are said to give a green color with ferric chloride solution and also a stronger color with sodium 2-naphthol-4-sulfonate than do the corresponding indoles (Kawana et al, 1965).

A more specific spot test for hydroxylamines, including the cyclic ones, is provided by reaction with triphenyltetrazolium chloride (T.T.C.) which, in the presence of alkali, give a characteristic purple-red color. This seems to be a specific reaction (Snow, 1954) and by its means the presence or absence of hydroxylamine can usually be safely deduced (Rogers, 1955). These investigators and others (Zinner and Kliegel, 1966; Thesing and Sirren, 1959; Brown et al, 1959) used this test to follow the progress of reactions which involve hydroxylamines. Feigl (1966), however, considers hydroxylamine to be completely inactive towards this reagent. It should also be remembered that other substances, such as sugars and ascorbic acid give a positive test with T. T. C. (Feigl, 1966).

The separation of some cyclic hydroxylamines from their corresponding amines as well as from some related nitroxides can be achieved by means of thin-layer chromatography. Weil (1968) developed some useful solvent systems for this purpose. Iodine vapor or potassium permanganate solution were used for detection and were found to be more useful than T. T. C. which gave only very faint pink spots.

Although a number of methods have been developed for quantitative estimation of aryl hydroxylamines (Boyland and Nery, 1964;

1964 a) and hydroxamine acids (Nery, 1966; Roncucci et al, 1971), there
is as yet no general method for analysis of cyclic hydroxylamines,
However, it is possible that these compounds could be determined
quantitatively by gas-liquid chromatography, after conversion into
suitably volatile ethers.

(C) Molecular Spectroscopy and Mass Spectrometry:

Ultraviolet spectroscopy: This technique was used by several
investigators (e.g.: Mcbeth and Price, 1936; Takahashi and Kano,
1963; Stacy et al, 1966) to study the tautomerism of cyclic N-hydroxy
compounds. In such cases, the position of maxima as well as their
intensities were compared with "fixed" models in which tautomerism
was not possible. Kawana et al (1965) also used the bathochromic
shift (5-10 mμ) showed by N-hydroxyindole derivatives, on addition
of alkali, as a method for confirming the presence of the N-hydroxy
function.

Infrared spectroscopy: This has proven to be more useful for both
identification purposes and tautomeric studies. Mousseron-Canet
and Boca (1967) as well as Kawana et al (1965) studied the i.r. spectra
of some 1-hydroxyindoles and found evidence for the existence of inter-
molecular hydrogen bonding. The simple compounds, N-methyl and
N,N dimethylhydroxylamine were also strongly hydrogen bonded
(Mansel and Spiers, 1959).

The presence of either or both the N-hydroxy and N-oxy
tautomers in any compound could be readily deduced from its infrared
spectrum and this was used to assign tautomeric equilibria in different
systems (Katritzky and Jones, 1960; Kloetzel et al, 1957; Mousseron-
Canet and Boca, 1967). Distinction between the N-OH and C-OH

functions is probably more difficult since both absorptions seem to be affected similarly by the same parameters (table 1). Their acetates or benzoates, however, are of particular advantage for identification purposes since electronegative groups attached to the oxygen atom of carboxylic acids are known to raise the stretching frequency of the carbonyl group by 15-70 cm^{-1} depending on the group (Freeman, 1958). The most pronounced shifts were observed with hydroxamic acids but also all compounds where the oxygen substituent was attached to nitrogen showed abnormally high frequency carbonyl absorptions. As expected, the N-benzoate esters absorb at a lower frequency ($\sim$1770 cm^{-1}) than the N-acetate ($\sim$1800 cm^{-1}) but still much higher than the ordinary benzoates ($\sim$1720 cm^{-1}) (see table 1).
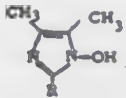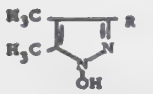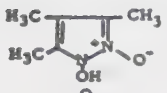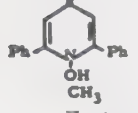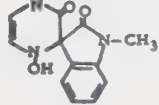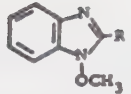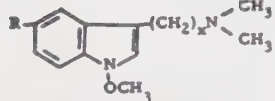
Nuclear magnetic resonance spectroscopy; This technique has been employed more frequently for detecting the N-hydroxy function as well as for studying the tautomerism of N-hydroxy compounds (Bonnet and McGreer, 1962; Acheson et al, 1968, 1970; Schweizer and Kopay, 1972). Also Mousseron-Canet and Boca (1967) used this method for quantitative determination of both tautomers of some N-hydroxyindole derivatives.

With few exceptions, studies showed that the N-hydroxy-proton resonance is detected at low field even in the absence of intra-molecular hydrogen bonding (table 1). Acheson et al (1970) detected the N-hydroxy proton in 1-hydroxy-2-methylindole at $\delta\sim$9.00 and reassigned the resonance at $\delta\sim$6.00, attributed earlier (Mousseron-Canet and Boca, 1967) to this proton, to the 3-hydrogen atom of the indole. The N-methoxy function might also be detected with n.m.r. spectroscopy since the methoxy group is attatched to an electro-

Table 1: Infrared absorption maxima and n.m.r. chemical shifts (relative to TMS) of some cyclic hydroxylamines and their methyl and acyl derivatives.

Structure	ν		δ		Ref.
	OH	C=O (ester)	OH	OCH₃	
CH₃ CH₃ N—OH*	3600-3000				1
, benzoate*		1740			2
[piperidine N-OCOPh]		1762 (liq)			2
		1766 (CCl₄)			3
[dihydropyridine N-OH, Ph, H]	3400-2400 (mull)		8.72 (CDCl₃)		4
			9.2		5
, benzoate		1759			6
Ph O H₃C N-OH morpholine		1755			4
	3600		3.3		7
[indole N-OH, R]					
R= CH₃	3510-3498 (CHCl₃)		~6.00		8
	3450 (KBr)				8
			9.75		9
			8.3-8.94		9
, p-chlorobenzoate		1775			10
R= Ph	2400, 3250 (br.)		8.85 (CDCl₃)		11
	2430 (v.br.)				12
, acetate		1772			11
, benzoate		1760			13
R= COOH	3225				11
, acetate		1800			11
, benzoate		1783			11
R= COOCH₃	3180				11
				4.2	14
, acetate		1802			14
, benzoate		1778			11
[indole R, COOC₂H₅, N-OH]					
R= CN	3260				15
			9.5-10.5 (dioxane)		9
R= CONH₂	3350, 3150				15
, acetate		1800			15
Ph R N-OH					
R= Ph	3320 (nujol)		not detected (CDCl₃)		16
, acetate		1700 (nujol)			16
, benzoate		1760 (nujol)			16

48

Structure	ν		δ		Ref.
	OH	C=O (ester)	OH	OCH$_3$	
R = COOC$_2$H$_5$	3370 (nujol)		10.2 (CDCl$_3$)		16
R = H			10.1 (CDCl$_3$)		16
			13.33 (CDCl$_3$)		17
, benzoate		1730			18
			8.5		19
, p-nitrobenzoate		1790			20
			15.8		21
	3636 (CHCl$_3$)				22
	3320				23
			4.1-4.2 (CDCl$_3$)		24
				4.09	25
				3.99	26

* are presented here for comparison.

References:

(1) Mansel and Spiers (1959)
(2) Freeman (1958)
(3) Zinner (1958)
(4) Coutts and El-hawari (unpublished)
(5) Kato and Yamanaka (1965)
(6) Kato et al (1967)
(7) Beckett and Salami (1972)
(8) Mousseron-Canet and Boca (1967)
(9) Acheson et al (1968)
(10) Acheson et al (1970)
(11) Kawana et al (1965)
(12) Sundberg (1965)
(13) Loudon and Tennant (1960)
(14) Baxter and Swan (1967)
(15) Loudon and Wellings (1960)
(16) Schweizer and Kopay (1972)
(17) Allan and Allan (1964)
(18) Akagane et al (1969)
(19) Freeman and Gannon (1966)
(20) Freeman et al (1969)
(21) Freeman and Gannon (1969)
(22) El-koly et al (1962)
(23) Habib and Rees (1962)
(24) Takahashi and Kano (1966)
(24) Morimoto and Oshio (1965)
(26) Johns et al (1967)

negative atom. In the few reported examples (Table 1), the N-methoxy-protons resonate at a lower field (δ 4-4.2) than usually demonstrated by aromatic ethers ($\delta \sim 3.8$).

Mass spectrometry: Some cyclic N-hydroxy compounds were identified by their ability to lose OH⋅ radicals from their molecular ions (Acheson et al, 1970; Beckett and Salami, 1972; Schweizer and Kopay, 1972). A similar loss resulting from N-O bond cleavage might also be expected from O-substituted derivatives of N-hydroxy compounds but the indole (20) showed only a small fragment ion (3%) corresponding to the direct loss of OCH_3 radical from the molecular ion. However, the same spectrum demonstrated a strong peak due

(20)
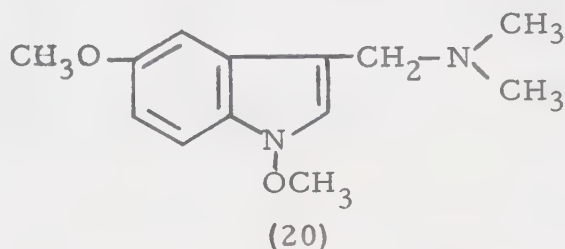
to the loss of OCH_3 from the $(M\text{-}NMe_2)^+$ ion. It is probable that this methoxy radical originated from the N-methoxy function and not from the aromatic ring (Johns et al, 1967).

(D) Stability:

Cyclic hydroxylamines and their alkyl and acyl derivatives vary greatly in their stability. Some show surprising stability and are isolated readily while others are very difficult to isolate and undergo oxidation, dehydration or rearrangement. Many of these compounds also dimerize, dehydrate or rearrange when heated with or without solvent. Thus, in refluxing cymene, 1-hydroxy-2-phenylindole (83) was converted to the dimeric indole (216) (Sundberg, 1965). Also,

(83)   (216)
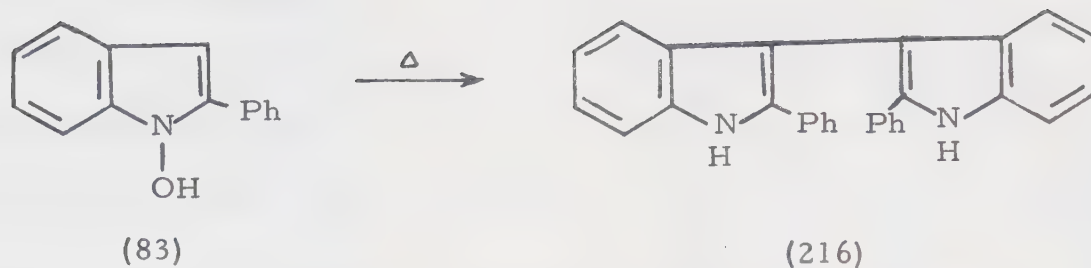
heating 1-hydroxy-2-phenyl-1,2-dihydropyridine (62a) to 200° or
boiling it with acetic anhydride resulted in dehydration to 2-phenyl-
pyridine (Kato and Yamanaka, 1965). The N-hydroxyimidazole (217)
rearranged to the imidazolone (218) upon heating to 235° (Volkamer
and Zimmermann, 1969).

(217)   (218)
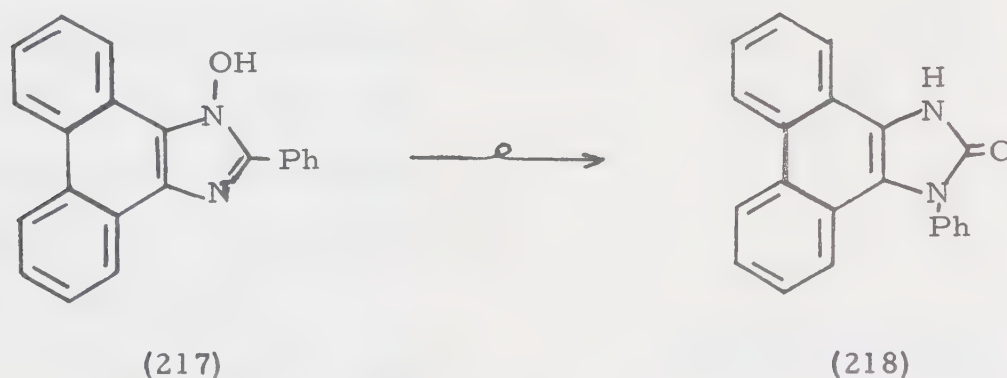
Upon alkylation, some N-hydroxydihydrotriazines (17)
yielded rearrangement products (219). When the N-alkoxy derivatives
(17, OCH_2R for OH) were isolated, they converted smoothly into (219)
by heating with or without solvent. The N-hydroxy compounds (17) did
not rearrange on heating (Mamalis et al, 1965).

(17)   (219)
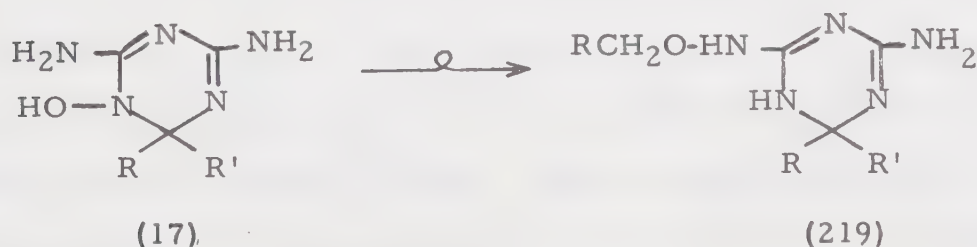
The tautomeric behavior of some N-hydroxyindoles (7) was studied by Mousseron-Canet and Boca (1967). N-Hydroxyindole (7, R=H) itself was found to exist solely as 3H-indole N-oxide (7b) whereas the 2-substituted derivatives(7, R=CH$_3$ or Ph) were tautomeric mixtures.

(7a)   (7b)

The N-oxide form (7b) is favored in solvents which are capable of strong hydrogen bonding. For 1-hydroxy-2-methylindole (7, R=CH$_3$), the proportion of each tautomer has been quantitatively estimated from the n.m.r. methyl integral. In deuterochloroform, methyl 1-hydroxyindole-2-carboxylate (224) exists as such while 5-bromo-1-hydroxyindole-2-carboxylic acid is present entirely in the 1-oxide

(224)   (225)
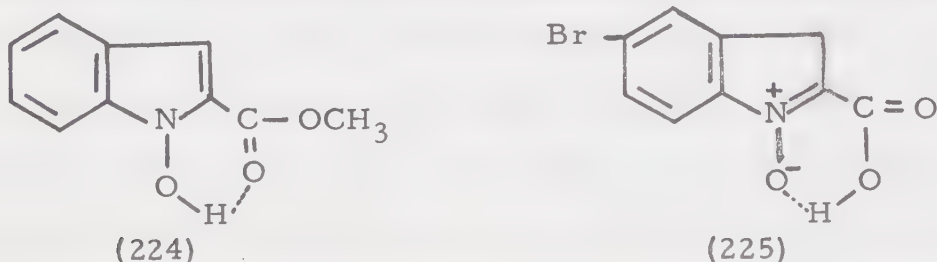
form (225) in the same solvent. These results were attributed to intramolecular hydrogen bonding (Acheson et al, 1968).

Similar studies have been reported on the tautomerism of 1-hydroxypyrroles (Kloetzel et al, 1957; Bonnett and McGreer, 1962; Schweizer and Kopay, 1972), 1-hydroxyimidazoles (Akagane et al, 1969), tetrahydropyridine 1-oxides and dihydro-1,4-oxazine 4-oxides (Elsworth and Lamchen, 1968). The two tautomers (157a ⇌ 157b) of certain triaryl-1-hydroxyimidazoles were claimed to be isolated under

(157a)   (157b)

controlled conditions (Volkamer and Zimmermann, 1969).

The structure of 1-hydroxybenzimidazole (226) evoked
some controversy. Kew and Nelson (1962) suggested the N-oxide form
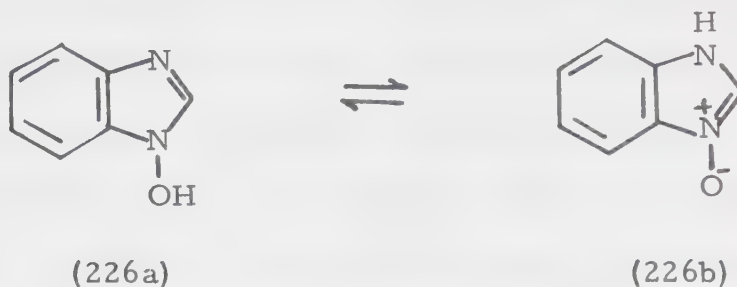
(226a)   (226b)

(226b) for this compound but Takahashi and Kano (1963) showed, by
using u.v. spectroscopy that a solvent-dependent tautomeric equili-
brium (226a ⇌ 226b) existed between the two forms. Hayashi et al
(1960) reported earlier what was considered to be a chemical evidence
for such tautomerism; reaction of 1-hydroxybenzimidazole (226) with
diazomethane yielded a mixture of the alkyl derivatives (227) and (228).

(227)   (228)
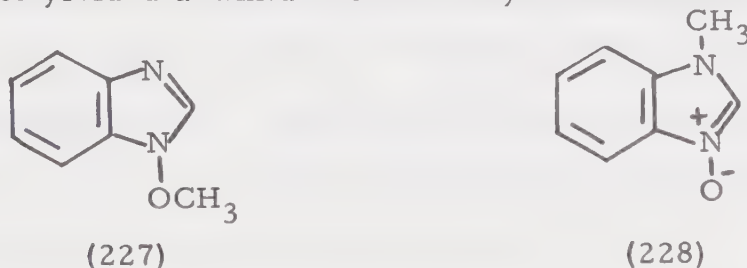
A solvent-dependent tautomerism was also observed with 1-hydroxy-6-
nitrobenzimidazole (Neadle and Pollitt, 1967) while 1-hydroxy-2-phenyl-
benzimidazole was shown to exist entirely as the N-hydroxy form even in
aqueous solution (Stacy et al, 1966). 1-Hydroxybenzotriazole
derivatives (229a) also behaved similarly; some are tautomeric

(229a)   (229b)

mixtures (229a ⇌ 229b) while others exist only as the N-hydroxy

structure (229a) (Macbeth and Price, 1936).

Studies using physical methods indicated that both tautomers

of 1-hydroxy-4-pyridone (230) are of comparable importance (Katritzky

and Logowski, 1971a).   Similarly, 10-hydroxyacridone exists in equi-

librium with equal amounts of 9-hydroxyacridine 10-oxide (Ionescu

et al, 1966).   In contrast, amino N-oxide exist predominantly in the

(230)   (231)
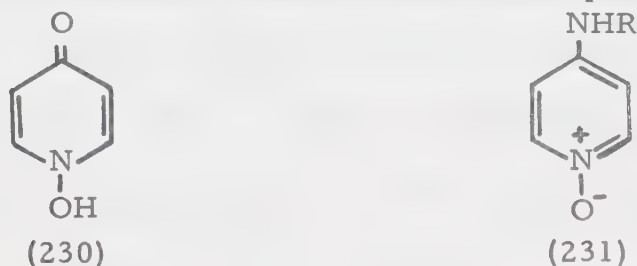
amino form (231) (Katritzky and Logowski, 1971b).   In certain

instances, however, chemical reactions gave products derived from

the N-hydroxy tautomer of amino N-oxides.   Alkylation and benzoyla-

tion of 2-aminopyrroline 1-oxide (232) occurred at the oxygen atom

giving products of the type (233) while acetylation gave only the N-acetyl

derivative (Forrester and Thomson, 1963).

(232)   (233)

(F) <u>Oxidation</u>:

Cyclic hydroxylamines are readily oxidized by a wide variety of oxidizing agents. When an α-hydrogen is available, the products are mostly cyclic nitrones (235); otherwise, different

products are isolated.

The passage of oxygen (or air) into a solution of the N-hydroxy compound, in the presence of a catalyst such as copper-ammonia complex, is commonly employed, but sometimes fails to oxidize these compounds. This method was used for the oxidation of 1-hydroxypyrrolidines such as (236) to the corresponding nitrones (237) (Bonnett <u>et al</u>, 1959). Similar results were obtained when

alkaline potassium ferricyanide (Brown <u>et al</u>, 1959b) or yellow mercuric oxide (Thesing and Sirrenberg, 1959) were used as oxidizing agents. The latter reagent was also employed for the oxidation of N-hydroxypiperidine, N-hydroxymorpholine (Elsworth and Lamchen, 1968), 2-hydroxy-1,2,3,4-tetrahydroisoquinoline (Thesing and Mayer, 1957) and 1-hydroxybenzodiazepines (Sternbath and Reeder, 1961; Sulkowski and Childress, 1963; Hoffman-LaRoche, 1966) to the corresponding nitrones.

Other ring substituents can also be affected during the oxidation of the N-hydroxy function. 1-Hydroxy-2-methylpyrrolidine-2-carboxylic acid (238) undergoes oxidative decarboxylation during the

nitrone (239) formation (Brown et al, 1959).

(238)   (239)
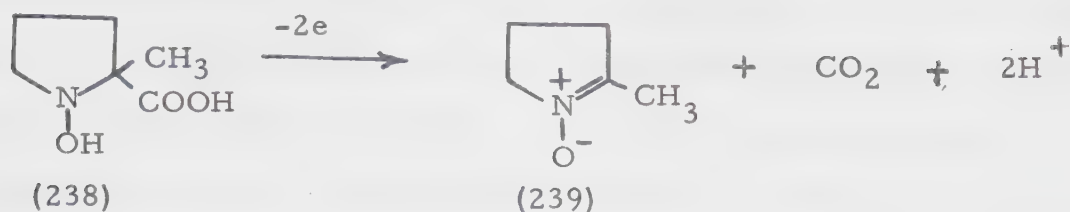
     1-Hydroxypiperidine (23) reacted with p-benzoqunione to yield a tetrahydropyridine 1-oxide-hydroquinone adduct (240) (Brown and Rogers, 1961). Aerial oxidation of the same N-hydroxy compound
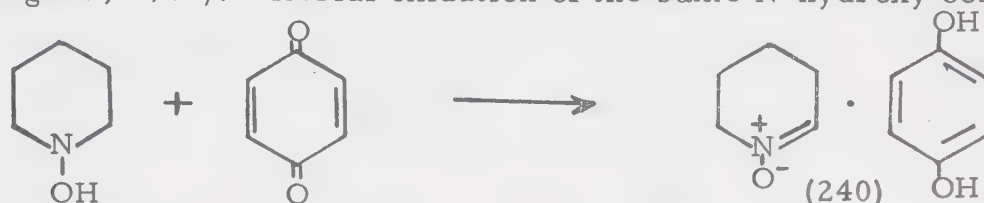
in the presence of cupric acetate yielded 3,4,5,6-tetrahydropyridine 1-oxide (241) which dimerizes immediately to the cyclic dimer (40) (Thesing and Mayer, 1956). A trimer formulated as (41) was formed by the oxidation of (23) using potassium ferricyanide (Thesing and Mayer, 1957). Related polymers were obtained by the oxidation of

(23)   (241)

(40)

(41)
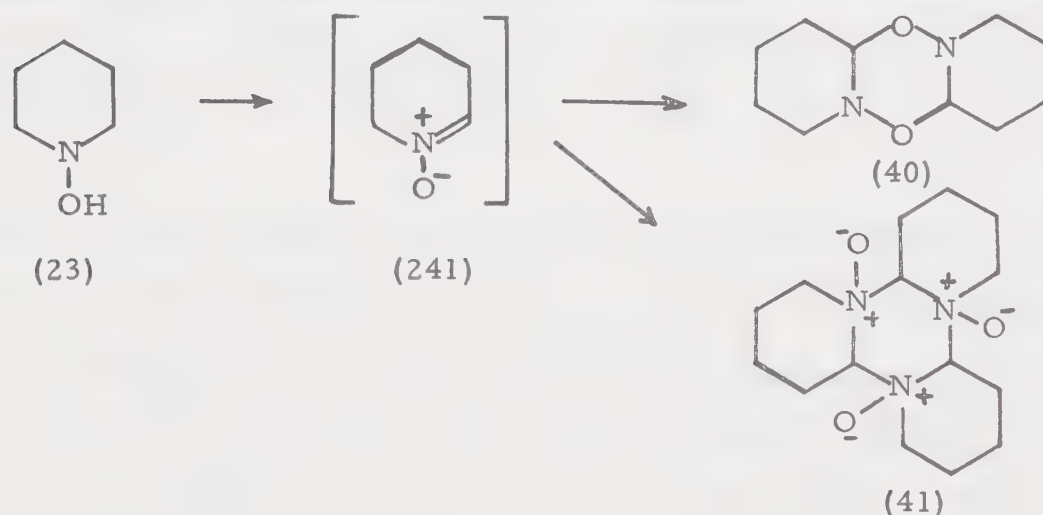
N-hydroxyhexaethyleneamine (Alford et al, 1966) and N-hydroxymorpholine (Elsworth and Lamchen, 1968).

     In some cases, the course of oxidation was found to depend

on subtle steric effects. Oxidation of 1-hydroxy-2-phenylpyrrolidine

(55) with mercuric oxide gave the nitrone (241) in which the nitrone

group is conjugated with the phenyl group (Thesing and Mayer, 1957,

Thesing and Sirrenberg, 1958). In contrast, the same reagent

oxidized 1-hydroxy-2-phenylpiperidine (242) to a dimer of the nitrone

(243) in which the nitrone group and the phenyl group are not conjugated

(Thesing and Mayer, 1957). This difference in the behavior of the

(55)   (241)   (242)   (243)
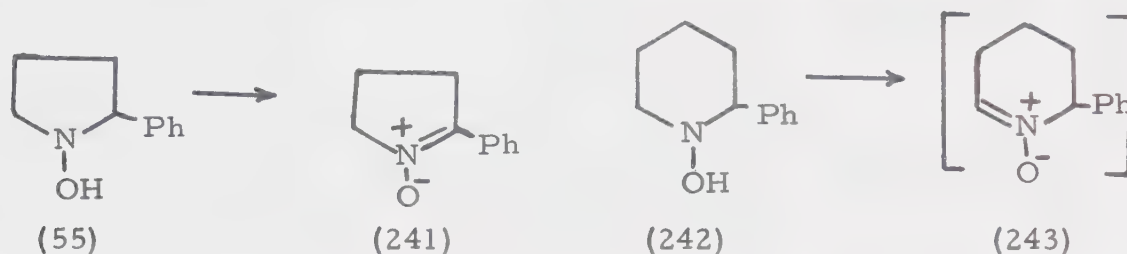
analogous N-hydroxy compounds (55) and (242) was explained in terms

of their stereochemistry (Thesing and Sirrenberg, 1959).

Ferric chloride is reported to oxidize the hydroxylamine

(244) to the corresponding hydroxamic acid (245) via the intermediate

(52) (Elsworth and Lamchen, 1966). The same reagent oxidized

(244)   (52)   (245)
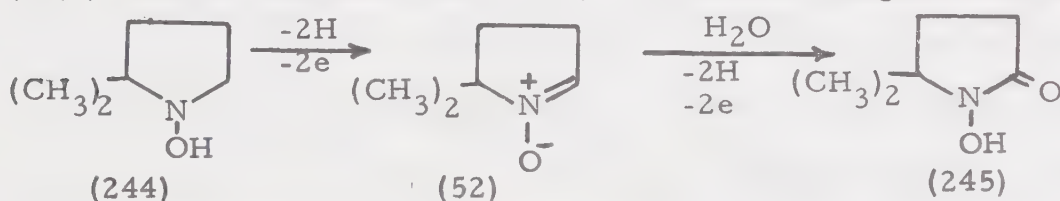
ethyl 1-hydroxyindole-2-carboxylate (7, R=COOEt) to the bis N-hydroxy

compound (246, R=COOEt) (Gabriel et al, 1923). A related product

(7) OH   OH   (246)   OH
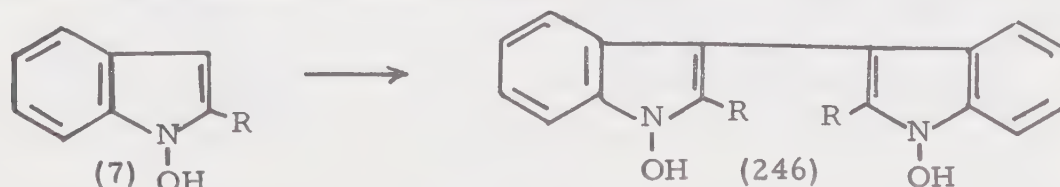
(246, R=Ph) was obtained by the oxidation of 1-hydroxy-2-phenylindole

(7, R=Ph) with nitrobenzene (1 mole) or diethylazodicarboxylate (2.5

mole) (Colonna and Monti, 1962). The diradical (247) was formed

when (7, R = Ph) was treated with t-butyl hydroperoxide or diethylazo-
dicarboxylate. Oxidation with excess nitrobenzene gave in addition
to (247), another diradical (248) and a nitrone (249) (Colonna and

(247)   (248)   (249)
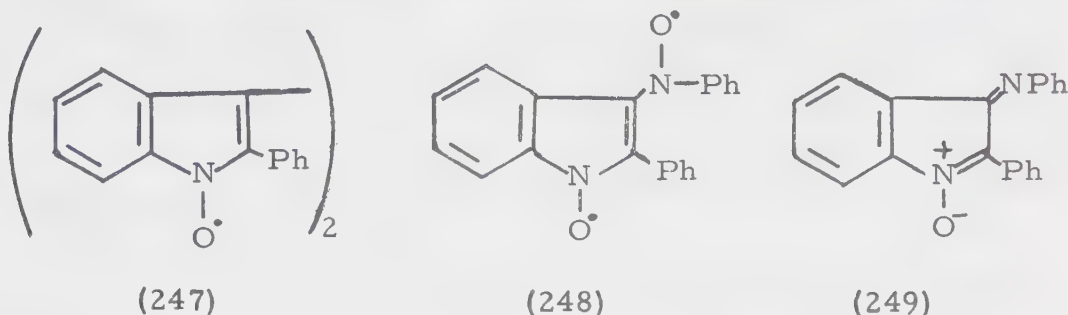
De Martino, 1963; Colonna and Bruni, 1964, 1965).

Other cyclic hydroxylamines are also reported to yield
free radicals on oxidation. 1-Hydroxyimidazole (157) gave the radical
(250) on treatment with halogens in polar solvents or with lead dioxide

(157)   (250)

(Volkamer et al, 1967; Volkamer and Zimmermann, 1969). The
stable free radicals (251) and (201) were also obtained by the silver
oxide (Rozantsev and Neiman, 1964) and catalyzed (Na_2WO_2) hydrogen
peroxide (Rozantsev and Shapiro, 1964) oxidation of the corresponding

(251)   (201)
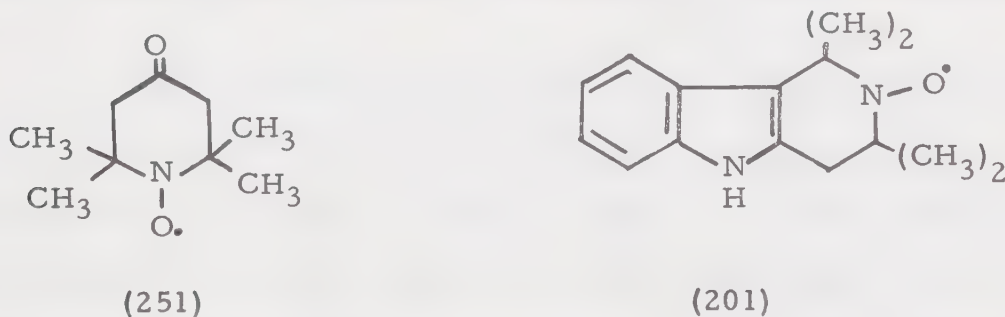
hydroxylamines. Oxidation of the N-hydroxypyrazole dimer (115)
with iodine yielded a compound (252) for which preliminary electron

spin resonance studies suggest biradical character (Freeman, 1973).

(115)   (252)
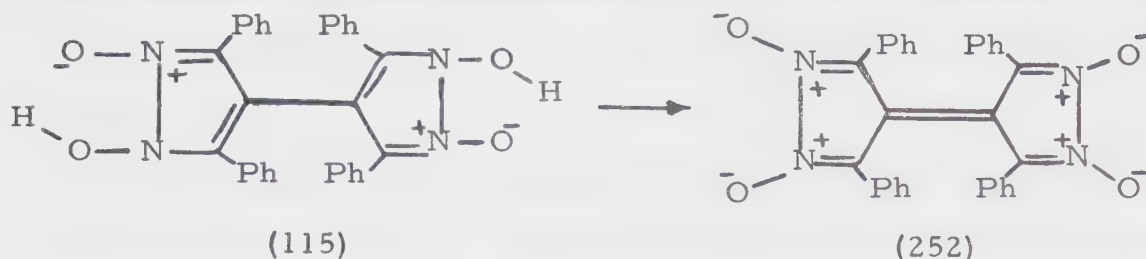
(G)   Reduction:

The N-hydroxy function as well as its O-substituted derivatives can be reduced by chemical reagents or by catalytic hydrogenation.   Zinc and acetic acid is used very frequently for this purpose.   N-Hydroxypyrazoles (Freeman and Gannon, 1969), N-hydroxyimidazoles (Busch, 1931), N-hydroxyindole (Loudon and Wellings, 1960) and N-hydroxypyrroles (Blaise, 1914; Blatt, 1934) were reduced to the corresponding amines by the use of this reagent. Phosphorous and hydroiodic acid were also used for the reduction of 1-hydroxybenzotriazole (Brady and Reynold, 1928) and 1,5-dihydroxy-3,3-dimethyl-piperidine (35) (Brown et al, 1959).

(35)   (253)
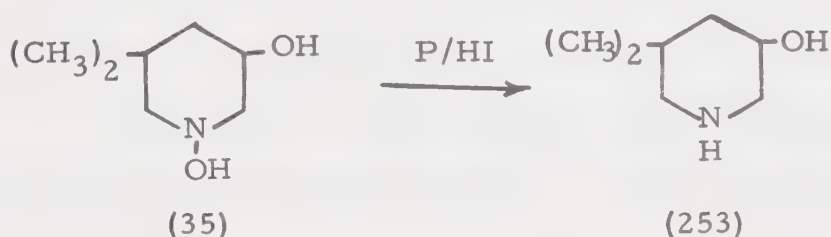
1-Hydroxyphenmetrazine (12) is said to reduce quantitatively to phenmetrazine (11) by means of titanous chloride or lithium aluminum hydride (Beckett and Salami, 1972).   The latter reducing agent was also used for the reduction of some substituted 1-hydroxy-imidazole derivatives (Volkamer and Zimmermann, 1969).   Other chemical reagents which have been used for the reduction of cyclic hydroxylamines include sodium hydrosulfite (Wright, 1964), tin and

hydrochloric acid (Curtius and Mayer, 1907), tin chloride and hydro-chloric acid (Minisci et al, 1963) and dimethylformamide (Taylor and Garcia, 1964).

The N-hydroxy function is, in most cases, susceptible to catalytic hydrogenation. N-Hydroxybenzimidazoles (Takahashi and Kano, 1963; Minisci et al, 1963) and N-hydroxyimidazole (Volkamer et al, 1967) were readily hydrogenated over suitable catalysts. In contrast, hydrogenation of the N-hydroxy compound (254) over Pd-C
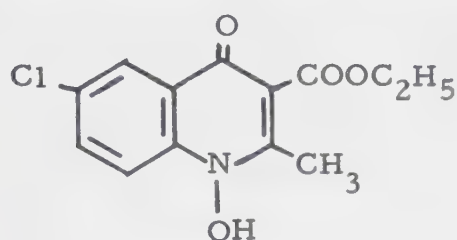
(254)
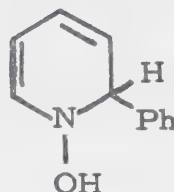
(255)

replaced only the chlorine atom with hydrogen without affecting the N-hydroxy function (Loudon and Wellings, 1960). Also, controlled catalytic hydrogenation of 1-hydroxy-2-phenyl-1,2-dihydropyridine (255) over Pd-C resulted only in the reduction of the pyridine ring giving 1-hydroxy-2-phenylpiperidine (Kato and Yamanaka, 1965).

Reduction of cyclic N-alkoxy compounds generally results in elimination of the N-alkoxy function. The N-methoxy compound (19) was successfully hydrogenated over Pd-C or reduced with lithium aluminum hydride to the corresponding amine (Morimoto and Oshio, 1965). Also, the N-alkoxy groups in (256) were eliminated by catalytic hydrogenation but the rate of elimination was slower than the rate of
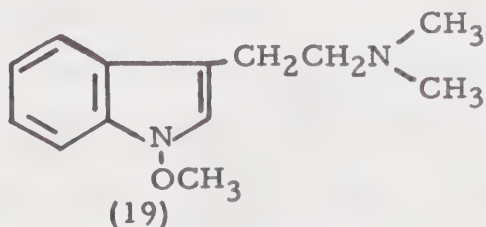
(19)
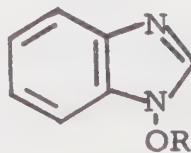
(256)

deoxygenation of the parent N-hydroxy compound (Takahashi and Kano, 1964). In certain cases, however, reduction does not affect the N-alkoxy function. For example, 1-methoxy-2-indole carboxylic acid was reduced with lithium aluminum hydride to yield 1-methoxy-2-hydroxymethylindole and 1-methoxy-2-formylindole; the N-methoxy function was not eliminated (Kawana et al, 1965).

Hydrogenation of acetates of structure (257) over Pd-C caused replacement of both the acetate group and the chlorine atom by

(257)   H₂/Pd-C →   (258)
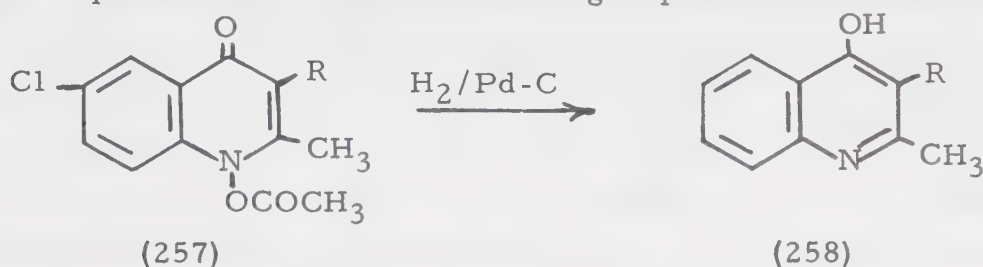
hydrogen (Loudon and Wellings, 1960). Sodium-amalgam also reduced the benzoate and sulfonate derivatives of 2-azanorbornenes (259) to (260), but when catalytic hydrogenation was carried out, only the double bond was reduced (Biehler and Fleury, 1971).

(259)   Na/Hg →   (260)

H₂/cat.

(261)
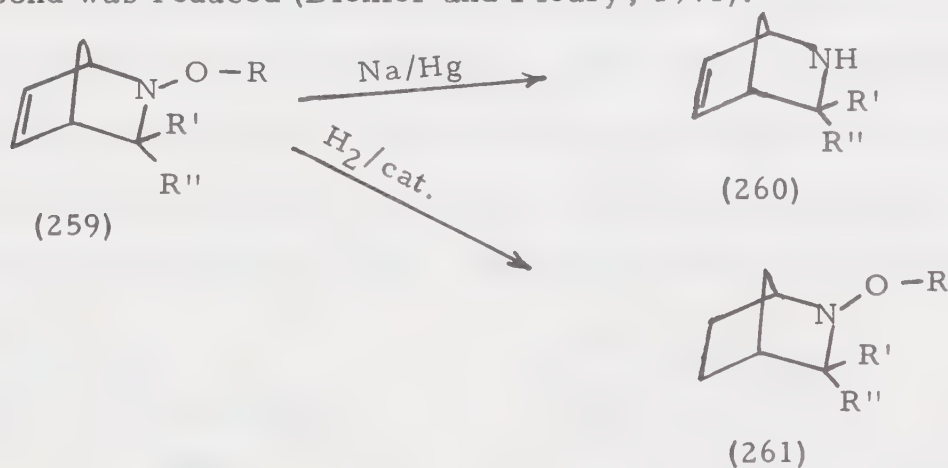
(H)   Alkylation Reactions:

Many N-hydroxy compounds are sufficiently acidic to be O-methylated with diazomethane (Hayashi et al, 1960; Baxter and Swan, 1967; Acheson et al, 1968). Dimethyl sulfate (Kliegel and

Fehrle, 1914; Brady and Reynolds, 1928; Taylor and Garcia, 1964)
and alkyl halides (Curtius and Mayer, 1907; Brady and Day, 1923;
Takahashi and Kano, 1964) are used more frequently for this purpose.
1-Hydroxybenzotriazole (146) reacted with dimethyl sulfate to give a
mixture of O-methyl (262) and N-methyl (263) derivatives, the ratio of
which was found to be alkali-dependent (Brady and Reynolds, 1931;
Brady and Jakobovits, 1950). In the absence of alkali and solvent,

(146)   (262)   (264)
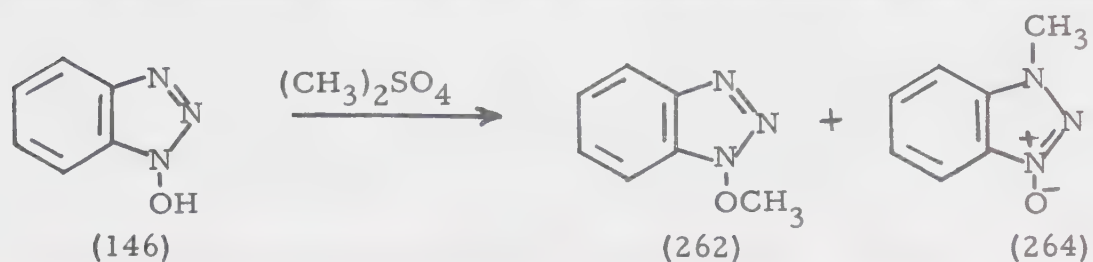
(146a) was converted only to the N-methyl compound (264), while a
better yield of the O-methyl derivative (263) was obtained when the
silver salt of (146) was methylated with methyl iodide (Brady and
Reynolds, 1928).

2,3-Dihydropyran reacted with methyl 1-hydroxy-2-indole-
carboxylate to yield (265) (Kawana et al, 1965). Similarly, dimethyl-
aminoethyl chloride gave the 1-alkoxy derivative (266) when it reacted
with 1-hydroxybenzimidazole in the presence of sodium hydride and
dimethylformamide (CIBA, 1966). In contrast, the reaction of 6-nitro-

(265)

$OCH_2CH_2N(CH_3)_2$

$CH_2CH_2COCH_2CH_3$

(267)
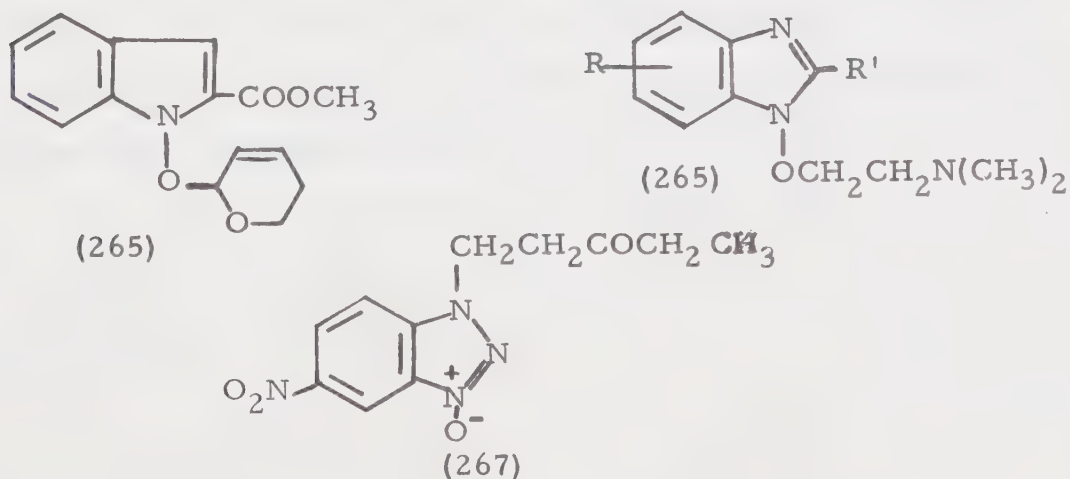
1-hydroxybenzotriazole with 1-chlorobutan-3-one yielded only the N-substituted product (267) (Shine et al, 1963).

Metabolic O-methylation of some carcinogenic hydroxyl-amines such as N-acetyl-N-2-fluorenylhydroxylamine (268) (Lotlikar, 1968) and hydroxamic acids such as 3-hydroxyxanthine (269) (Stöhrer, 1972) was performed in vitro using enzyme systems from rat liver or kidney. The methyl donor is S-adenosylmethionine (SAM); cysteine

(268)   (269)
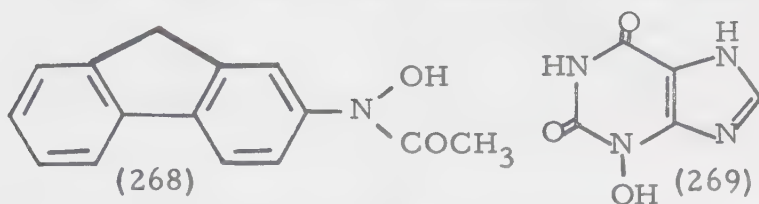
is sometimes required but divalent cations do not stimulate this reaction which appeared to be specific for N-hydroxy compounds (Weisburger and Weisburger, 1973). Both the O-methyl derivatives (268, OCH$_3$ for OH) and (269, OCH$_3$ for OH) were also synthesized, but it is not known yet whether these can react with nucleophilic compounds as the corresponding esters (acetates, glucuronides and sulfonates) do. Accordingly, the biological significance of this reaction is not yet established.

Several aldehydes react with cyclic N-hydroxy compounds to give O-semiacetals (270) which are converted to the so-called "mixed N,O-acetals" (271) and (272) when reacted with amines or hydrazines (Zinner and Kliegel, 1966). Treatment of the semiacetal (270) with arylisocyanates yielded (274) or a mixture of (274) and (273) (Zinner et al, 1965) while reaction of (270) with diphenyl boric acid gave 5-boro-1,2,4-dioxazole derivatives (275) (Zinner and Moll, 1966; Zinner and Kliegel, 1966).

X—N—OH

OCONHR'
|
X—N—O—CH
|
R

(273)

+/or

X—N—O—C—NHR'
          ‖
          O

(274)

R'NCO

RCHO

R'$_2$NH

R
|
X—N—O—CH—OH

(270)

HNR'—NR''$_2$

(Ph)$_2$B—OH

R
|
X—N—O—CH—NR'$_2$

(271)

R   R'
| /
X—N—O—CH—N
          \
           NR''$_2$

(272)

X—N   O
    \   /
     B   CH—R
    / \   /
   Ph Ph O

(275)
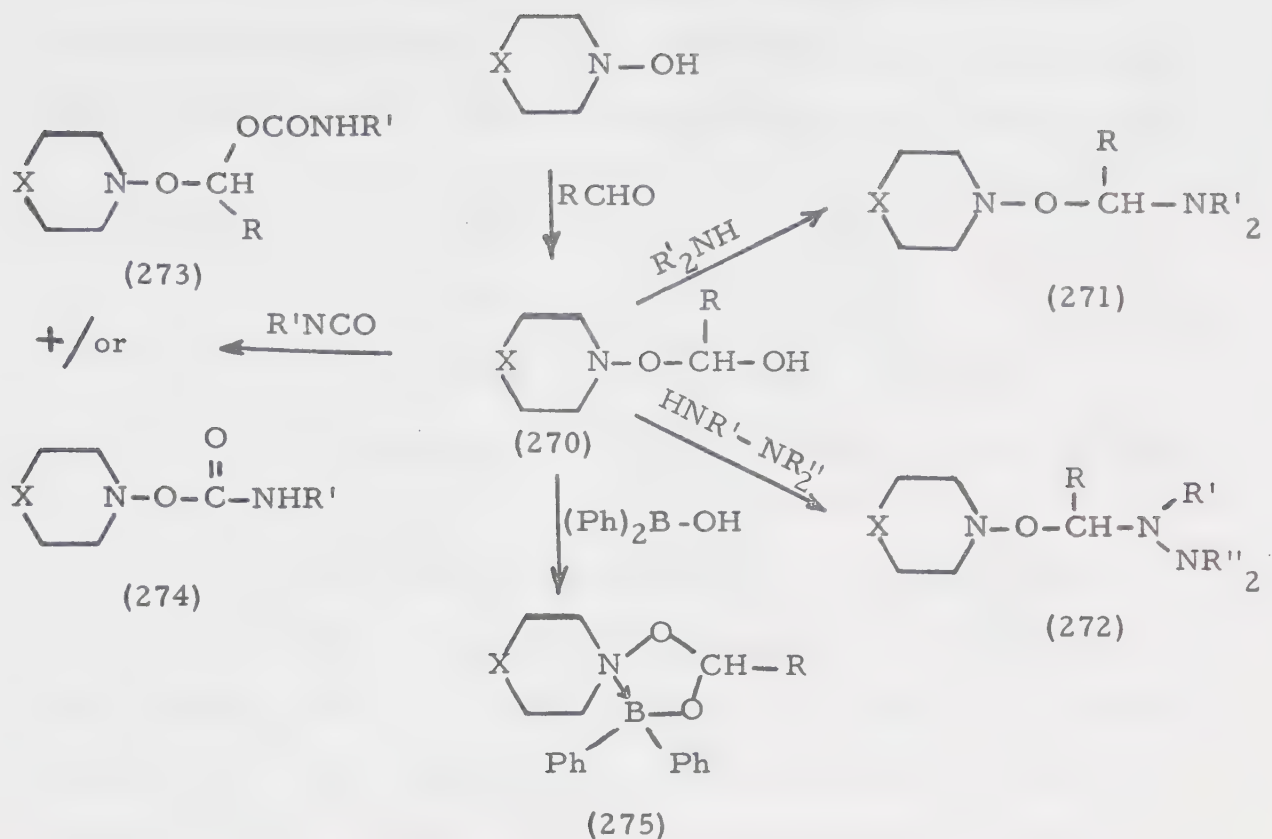
1-Hydroxypiperidine has been successfully condensed in a
Michael-type reaction with various electron deficient alkenes (RCH=CH$_2$;
R=COCH$_3$, COOR, CN) to produce adducts (276) (Zinner et al, 1965).
The N-hydroxy group also added across the triple bond of acetylene
dicarboxylic acid esters giving the adduct (277) (Winterfeldt and Krohn,
1969).   On the other hand, the reaction of 1-hydroxypyrrolidine (4)

N—OH

(23)

CH$_2$=CHR

C—COOCH$_3$
‖
C—COOCH$_3$

N—O—CH$_2$CH$_2$R

(276)

N—O—C—COOCH$_3$
       ‖
       HC—COOCH$_3$

(277)
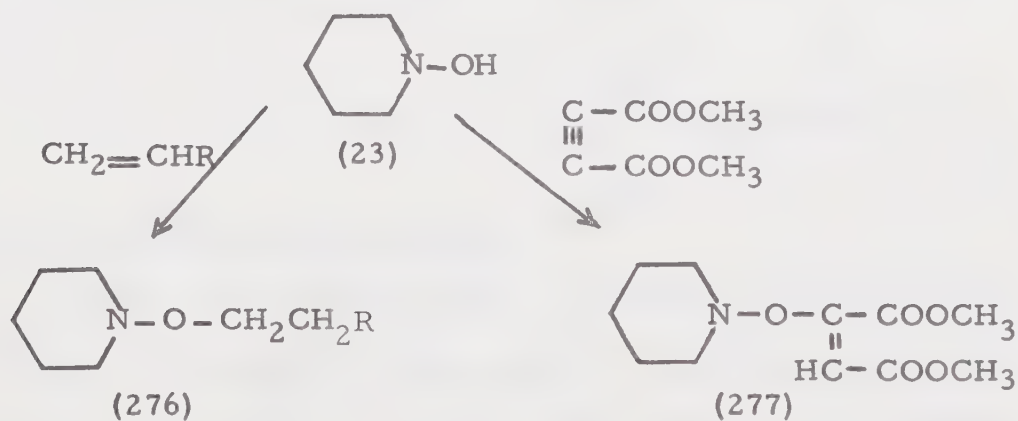
with 2- or 4-vinylpyridines (278) resulted in the loss of the oxygen atom and gave pyridylethylpyrrolidine (279) (Thesing and Sirrenberg, 1959). This "abnormal" Michael reaction was found to proceed in the

(4)   (278)   (279)
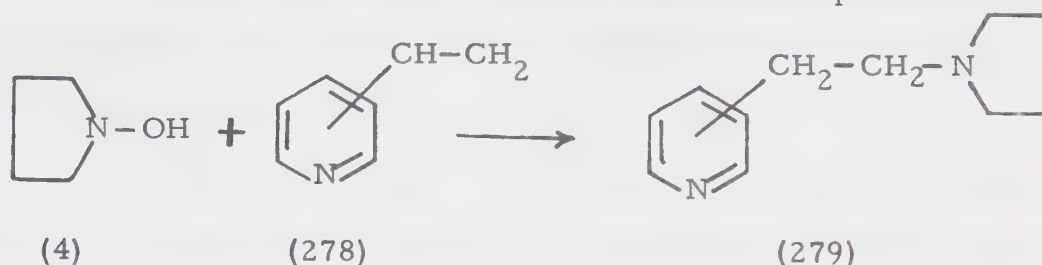
absence as well as in the presence of acidic (HOAc) or basic (Triton B) catalysts (Paquette, 1962).

Treatment of N-hydroxypiperidine (23) with propylene oxide was said to proceed via O-alkylation to give 1-piperidinoxy-2-propanol (280) (Zinner and Ritter, 1962). This report was discounted by Cannon et al (1969) who showed that the product was, in fact, the amine oxide (281). Based on this, the products obtained by the reaction of other N-hydroxy compounds with alkylene oxides (Zinner et al, 1965) would be worth a reinvestigation.

(23)   (280)

                                  (281)
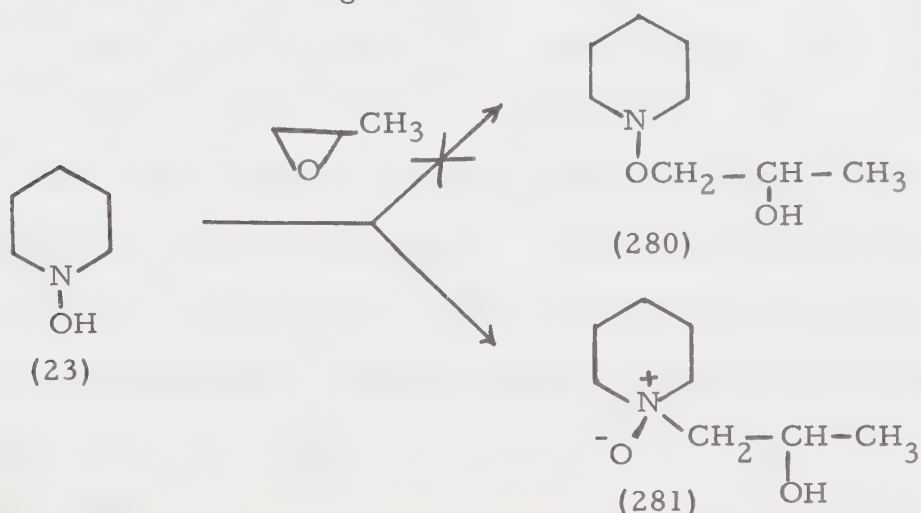
(I)   Acylation and Sulfonation Reactions:

Acetyl, benzoyl and sulfonyl chlorides react readily with cyclic N-hydroxy compounds to form acetate, benzoate and sulfonate derivatives. Acetic anhydride, benzoic anhydride as well as ketene

are also used for this purpose. Alternatively, cyclic acetoxy and benzoyloxy derivatives are obtained by the action of acetyl or benzoyl peroxide on the corresponding cyclic amines or by condensation reactions in which the acyloxy function is already present in one of the reacting components.

1-Acetyloxypiperidine was prepared by the action of acetyl chloride, acetic anhydride or ketene on 1-hydroxypiperidine (Zinner, 1957a). Similarly, treatment with benzoyl chloride yielded 1-benzoyl-oxypiperidine. Both these acyloxy derivatives were also prepared by reacting piperidine with the corresponding acyl peroxide (Gambarian and Kazaryan, 1933; Sammes, 1965; Zinner, 1958). Similar preparations of N-acetoxy and N-benzoyloxy derivatives of morpholine, indoles, imidazoles, pyrazoles, benzimidazoles and benzotriazoles are known; examples of these compounds are presented in table 1. There are cases, however, where dehydrated or rearranged products were obtained. For example, acetylation of 1-hydroxy-2-phenyl-1,2-dihydropyridine by heating with acetic anhydride gave only the de-hydrated product, 2-phenylpyridine (Kato and Yamanaka, 1965). Benzoylation of the same compound at low temperature was successful and yielded the O-benzoyl derivative. With 1-hydroxypyrazole 2-oxides (198), the acetyl and benzoyl derivatives (282) formed initially then rearranged to (283). In the absence of the N-oxide function, however, O-benzoyl derivatives could be isolated (Freeman and Gannon, 1969).

(198)   (282)   (283)
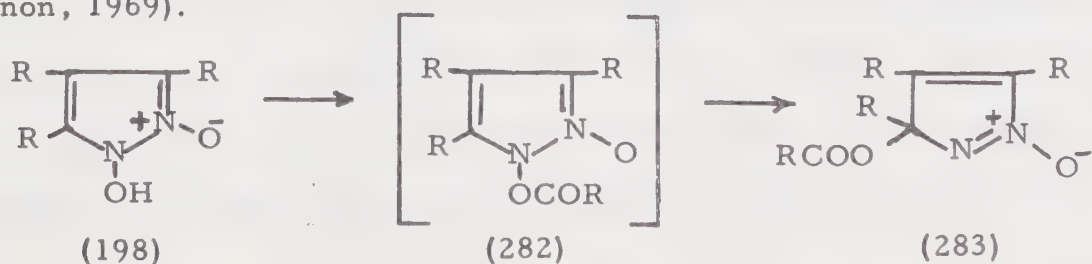
The N-hydroxycarboxylic acid esters (285) were prepared by the action of alkyl chloroformates on the N-hydroxy compounds (284) (Zinner, 1957; Zinner and Kliegel, 1966). Isocyanate derivatives also react with cyclic hydroxylamines to give N-carbamoyloxy

(284)   X=CH$_2$ or O   (285)
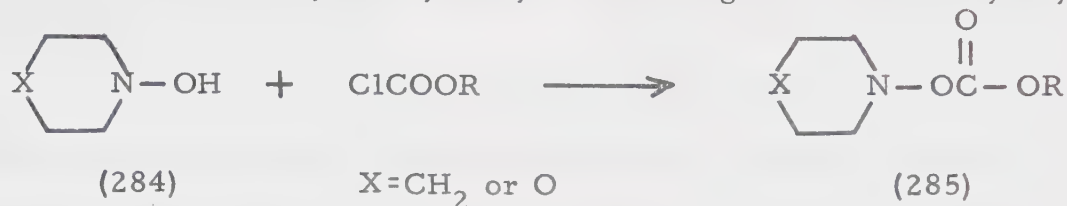
derivatives (287) (Zinner and Kliegel, 1966; Akagane et al, 1969).

(286)   RCNO   (287)
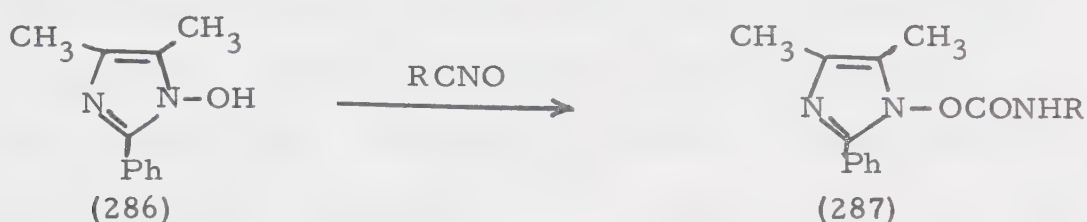
Sulfonate derivatives of N-hydroxy compounds are less stable than the corresponding acetates or benzoates and only a few O-sulfonates have been isolated. Zinner (1957, 1958, 1958a) described the formation of piperidine N-sulfonic acid (288) and piperidine N-oxysulfinic acid ethyl ester (289) by the interaction of 1-hydroxy-piperidine with sulfur dioxide and chlorosulfinic ester respectively. The stable tosylate (290) was also isolated (Freeman et al, 1959).

(288)   (289)   (290)
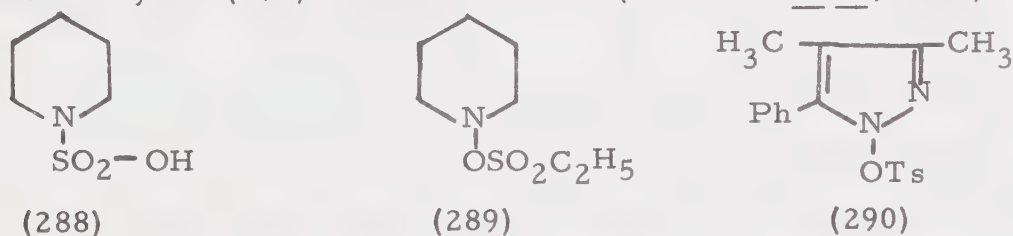
On the other hand, attempts to prepare the O-sulfonate derivative (291) by reacting (83) with p-toluenesulfonyl chloride gave a rearrangement product which was formulated as (292) (Sundberg, 1965). Similar rearrangements were also observed (Tanida, 1959; Gassman and Hartman, 1972) during attempted sulfonation of other N-hydroxy

(83)   (291)   (292)
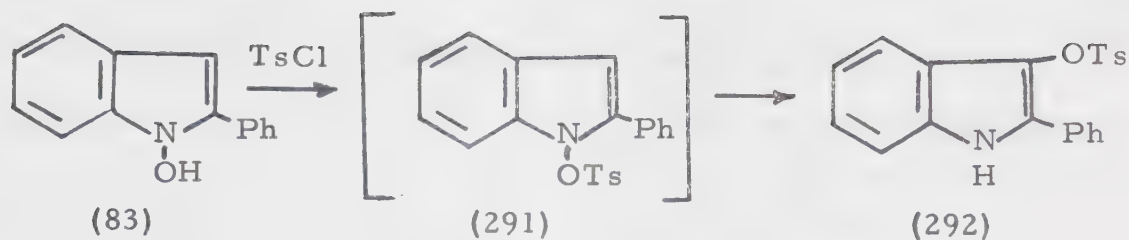
compounds.

The possibility of employing N-acyloxy derivatives of cyclic hydroxylamine as acylating agents was studied by Sammes (1965). N-Benzoyloxypiperidine was found to react with benzylamine and with ethyl aminoacetate to give N-benzylbenzamide and hippuric acid respectively. N-acetoxypiperidine was also shown to be a reactive acylating agent. Beaumont et al (1965) as well as Young and Handford (1967) have demonstrated the usefulness of these esters and other esters of N-hydroxypiperidine in peptide synthesis and as selective acylating agents.

(J)   Reactions with Nucleophilic Reagents:

The reactions of arylhydroxylamines and hydroxamic acids with different nucleophilic reagents including tissue nucleophiles (amino acids, proteins and nucleic acids) have been studied in great detail. However, only few of these reactions have been attempted with cyclic hydroxylamines or their alkyl, acyl or sulfonyl derivatives. The importance of these studies is to provide information on any interactions which might occur between cellular macromolecules and N-hydroxy compounds once they are metabolically formed in the body.

Clark-Lewis and Katekar (1959) found that ethanolic hydrogen chloride converted the N-oxide (293) to the spiro-quinoxaline derivative (296, R=H). When hydrogen chloride was replaced with acetyl chloride, the 1-acetyl derivative (296, R=COCH$_3$) was formed.

In view of the work on the interaction of phenylhydroxylamine with
chloride ions (Heller et al, 1951; Ingold, 1953), it was proposed that

(293)

(294)

(296)

(295)
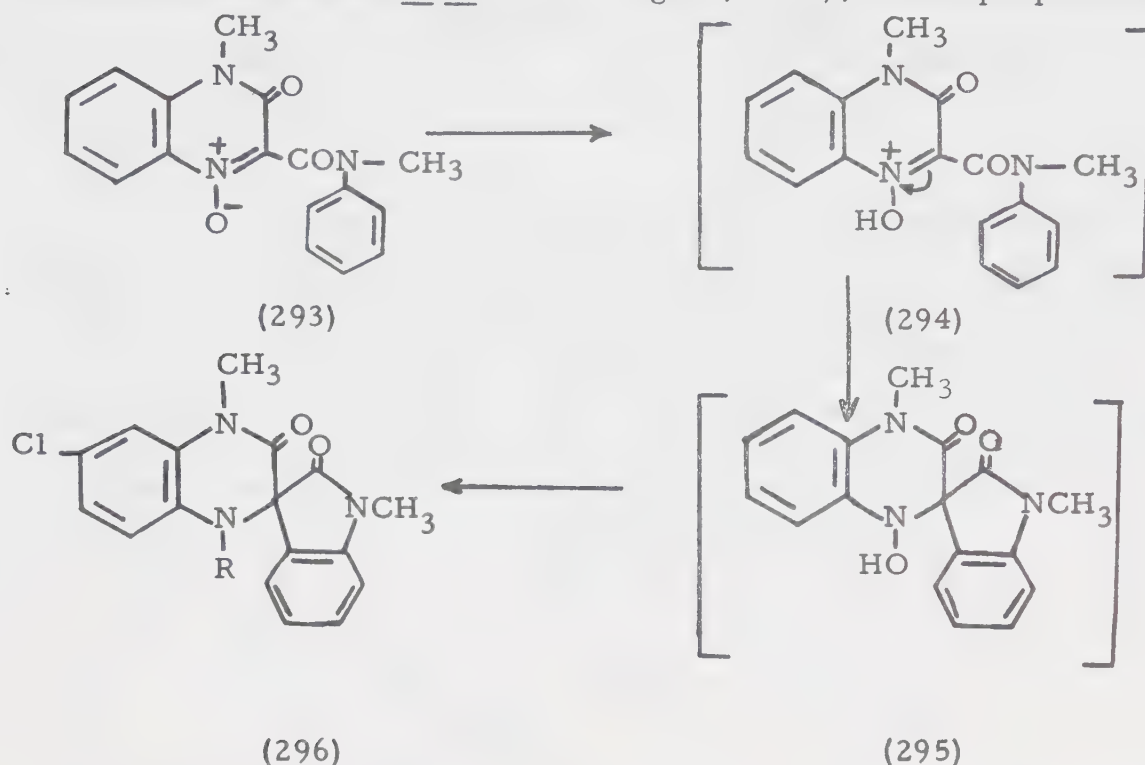
the conversion of (293) to (296) proceeded via an N-hydroxy intermedi-
ate (295). Attempts by Habib and Rees (1962) to prepare the latter
compound failed, although, as described earlier in this introduction,
they were able to prepare the structurally related N-hydroxypyrazine
(208) by the action of ethanolic hydrogen chloride on 3,4-dihydro-4-
methyl-2-(N-methyl-N-phenylcarbamyl)-3-oxopyrazine 1-oxide(207).
No chlorinated derivatives were isolated from this reaction. Similar-
ly, refluxing a crude product containing 1-hydroxyindole-2-carboxylic
acid with methanolic hydrogen chloride results in the formation of its
methyl ester without elimination of the N-hydroxy function (Baxter and
Swan, 1967). Also, treatment of the 1-hydroxypyrazole (296) with
lead tetracetate yielded the acetate derivative (297) in which the N-O
bond remained intact (Freeman and Gannon, 1966).

(296)   +   Pb(OCOCH$_3$)$_4$ $\longrightarrow$ (297)
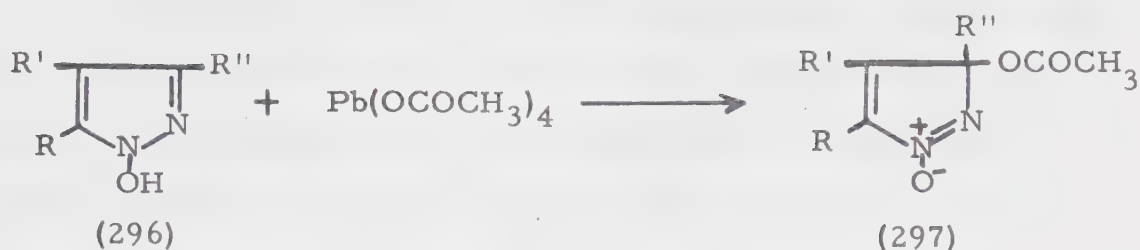
Heating 1-ethoxybenzimidazole (298) with hydrochloric or hydrobromic acids in a sealed tube, caused cleavage of the C-O bond of the ethoxy group giving N-hydroxyimidazole (276) (Takahashi and Kano, 1964).   On the other hand, the 2-alkoxy derivatives (299) were obtained when (298) was heated with sodium alkoxide.   The same

(298)

HCl / or HBr

ROH

(226)   (299)
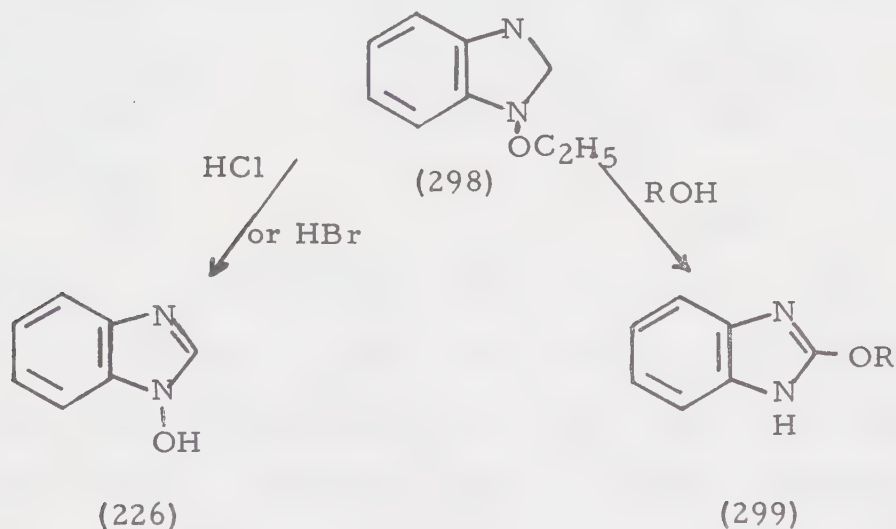
N-ethoxy compound (298) reacted with nucleophilic reagents such as hydrazine hydrate and sodium hydrogen sulfite to give 2-hydrazino-benzimidazole and sodium 2-benzimidazolesulfonate respectively, but it did not react with potassium cyanide except at elevated tempera-ture to give a poor yield of 2-benzimidazole carbamic acid.   In these reactions, it was assumed that a nucleophilic reagent attacked the electron deficient 2-position of 1-alkoxybenzimidazoles, then elimination of alcohol occurred to give 2-substituted benzimidazoles (Takahashi and Kano, 1964).

Biochemically, glucuronide, sulfonate and acetate esters were found to be more reactive with tissue nucleophiles than their parent N-hydroxy compounds. Although enzymic O-acetylation of foreign compounds containing hydroxyl groups could not be demonstrated, O-acetate derivatives such as (300) and (302) have been used as model derivatives of their respective potential glucuronide or sulfonate conjugates. Compound (300) reacted in vitro with chloride ion or methionine to give 8-chloroxanthine (201, R=Cl) and 8-methyl-mercaptoxanthine (301, R=SCH$_3$) which are identical to two urinary

(300)   (301)
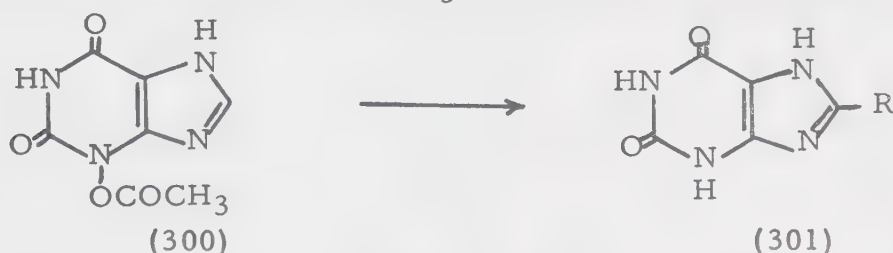
metabolites of 3-hydroxyxanthine (Stöhrer and Brown, 1970). This reaction with methionine is reminiscent of the well studied (Lotlikar et al, 1966; Miller et al, 1966; Irving, 1970) interaction of the carcinogenic model compound N-acetoxy-N-acetyl-2-aminofluorene (302) with tissue nucleophiles. A proposed mechanism of the interaction of (302) with methionine is shown in scheme 1 (Miller and Miller, 1969).
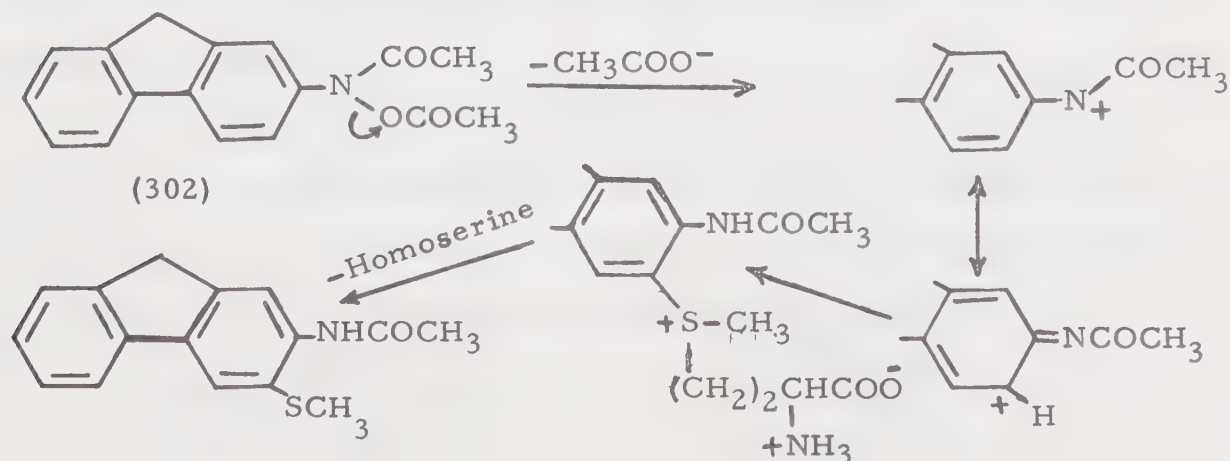
Scheme 1

(K)   Reactions with Electrophilic Reagents:

The reactions of 1-hydroxy-2-phenylindole (83) with a number of electrophilic reagents were studied by Colonna and his co-workers.   Treatment of (83) with aromatic nitroso compounds gave 2-phenyl-3-aryliminoindole 1-oxide (303) (Colonna and Bruni, 1967, 1967a).   An adduct of 1-hydroxy-2-phenyl-3-(phenylazo)indole (304) with (83) was formed when the latter was treated with phenyl-

(303)   (304)   (305)
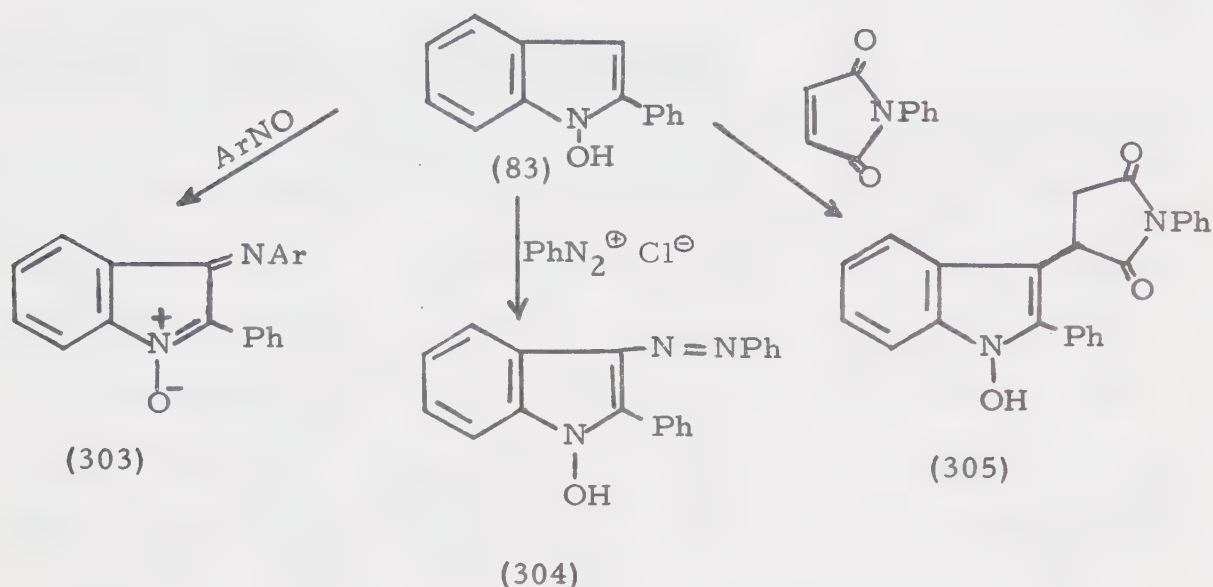
diazonium chloride (Colonna and Bruni, 1964).   The same N-hydroxy compound (83) reacted with some dienophiles such as N-phenylmaleimide to yield 1-hydroxy-2-phenyl-3-(N-phenylsuccinimidyl)indole (305) (Colonna and Monti, 1962).

1-Hydroxypyrazole 2-oxides (198) reacted with nitrous acid in an electrophilic substitution reaction followed by oxidation with the excess acid to yield nitropyrazolenine 1,2-dioxides (306) (Freeman and Gannon, 1969).   In a similar reaction, 1-ethoxybenzimidazole

(198)   (306)
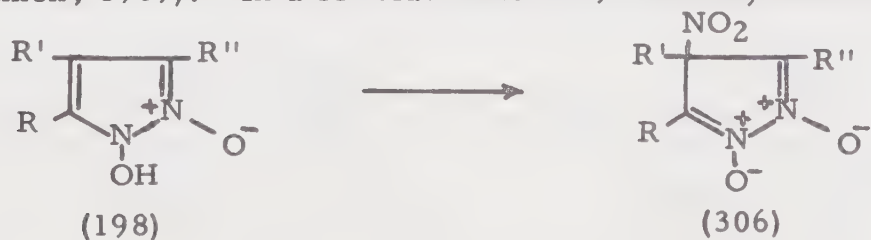
gave a mononitro derivative (307) when treated with a mixture of fuming nitric acid and sulfuric acid at room temperature and a dinitro derivative (308) on heating (Takahashi and Kano, 1964).
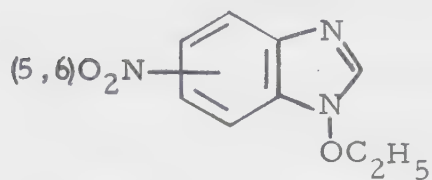
(307)
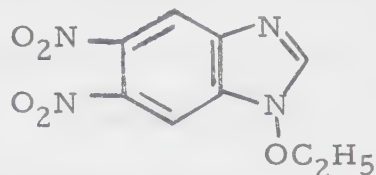
(308)

SCOPE OF THE PRESENT INVESTIGATION.

The preparation of some novel cyclic N-hydroxy compounds was the primary objective of the research described in this thesis. Assumming that these compounds could be obtained, a study of some of their chemical and pharmacological properties was also desirable in order to help understand the recent flow of biochemical studies in this area. This problem was approached by attempting the reductive cyclization of some aromatic nitro compounds which have a side chain with a carbonyl group suitably orientated with respect to the nitro group. Coutts and his co-workers (Coutts and Wibberley, 1963; Coutts, Noble and Wibberley, 1964; Coutts, Peel and Smith, 1965; Coutts, Barton and Smith, 1966; Coutts and Hindmarsh, 1966; Coutts and Smith, 1967). have shown that this type of compound can be reductively cyclized by sodium borohydride and palladium-charcoal and although under normal conditions, aromatic nitro compounds are normally reduced to amines, o-nitro esters e.g. (309), gave good yields of cyclic hydroxamic acids (310). This might be the most reliable method for the reductive cycli-

(309)

(310)

zation of a nitro ester to a hydroxamic acid (Bapat et al, 1969). The formation of cyclic N-oxy and N-hydroxy compounds by using the same reduction system has also been described (Coutts and Wibberley, 1963).

The reduction of 4-(2-nitrobenzylidene)-2-pyrazolin-5-ones (98), compounds which possess a lactam carbonyl group, was investigated by Coutts and Edwards (1966). These authors claimed that these compounds cyclized to N-hydroxypyrazoloquinoline derivatives (99) when reduced with cyclohexene and palladium-charcoal; the catalyzed sodium borohydride reductions were less successful. This work was reinvestigated in this present study and this has shown that the products were not N-hydroxy compounds. The method was modified and other reduction systems were also used until some cyclic N-hydroxyindolines were successfully prepared. These were characterized and a study of their chemical reactivity was undertaken. The mass spectra of these compounds as well as the mass spectra of some pyrazolone derivatives were also recorded and examined. During these reductions, other compounds including spiro-(tetrahydroquinoline)pyrazolones were also obtained and characterized.

These results suggested a reinvestigation of the reductions of 4-(2-nitrophenylthio)-2-pyrazolin-5-ones (400) which was claimed (Pound, 1970) to have yielded N-hydroxybenzothiazines (402). The same products described by Pound (1970) were isolated but were also found not to be N-hydroxy compounds.

DISCUSSION

PART 1: REDUCTION OF SOME 4-(2-NITROBENZYLIDENE)-2-PYRAZOLIN-5-ONES

Introduction:

The value of using sodium borohydride/palladium-charcoal for the reductive cyclization of some aromatic nitro compounds which possessed an acidic or an ester group in a position capable of under-going cyclization has already been discussed. Coutts and Edwards (1966) tried this method, among others, to reduce aromatic systems which possessed suitably orientated nitro and lactam carbonyl groups in order to obtain some novel cyclic N-oxides or N-hydroxy compounds. They prepared a series of 4-(2-nitrobenzylidene)-2-pyrazolin-5-ones (98) and reduced them using several methods which were known to yield N-oxides or N-hydroxy compounds in certain instances. The cyclic N-hydroxy compounds, 9-hydroxypyrazolo[3,4-b] quinolines (99) were reported to be among the reduction products obtained (Coutts and Edwards, 1966).
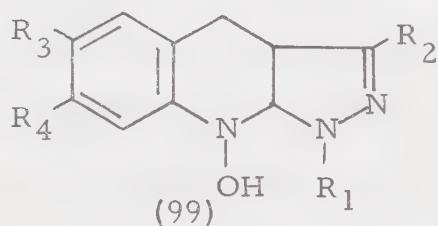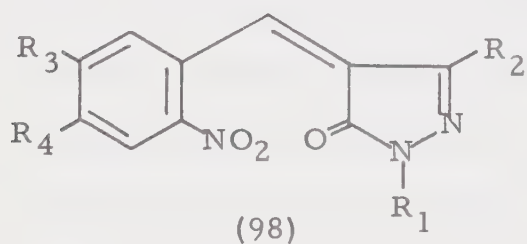
	R_1	R_2	R_3	R_4
a;	C_6H_5	CH_3	H	H
b;	C_6H_5	C_6H_5	H	H
c;	C_6H_5	CH_3	Cl	H
d;	C_6H_5	CH_3	OCH_3	OCH_3

	R_1	R_2	R_3	R_4
e;	C_6H_5	CH_3	O-CH$_2$-O	
f;	H	CH_3	H	H
g;	$COCH_3$	CH_3	H	H

One of these reduction products (99a) was previously claimed (Narang et al, 1934) to be a product of the reduction of (98a) by either aluminum amalgum, zinc dust and acetic acid or alcoholic hydrochloric acid.   Narang et al (1934) suggested that this reduction proceeded through the hydroxylamine compound (315) which they also claimed to have isolated.

(315)

As this present investigation was aimed mainly at the preparation of some cyclic N-hydroxy compounds to study their chemical behavior and evaluate their pharmacological activity, this reported work was reinvestigated first.

Preparation of some 4-(2-nitrobenzylidene)-2-pyrazolin-5-ones (318a-c).

The three 2-nitrobenzylidene derivatives chosen for this investigation were: 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one(318a), 4-(2-nitrobenzylidene)-1,3-diphenyl-2-pyrazolin-5-one(318b) and 4-(5-chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one(318c).   These were prepared by a known method (Coutts and Edwards, 1966) which involved heating of o-nitrobenzaldehyde (316a) or 3-chloro-6-nitrobenzaldehyde (316b) with the appropriate pyrazolone derivatives (317) in acetic anhydride containing anhydrous sodium acetate.

(316) a; R = H

b; R = Cl

(317) a; R = CH$_3$

b; R = C$_6$H$_5$

(318) a; R = CH$_3$, R'=H
b; R = C$_6$H$_5$, R'=H
c; R = CH$_3$, R'=Cl

One of the pyrazolones required for this synthesis, 3-methyl-1-phenyl-2-pyrazolin-5-one (317a) was available commercially and the other, 1,3-diphenyl-2-pyrazolin-5-one (317b) was prepared by the interaction of ethylbenzoyl acetate with phenylhydrazine.

Reduction of the O-nitrobenzylidene derivatives (318a-c) with sodium borohydride and palladium-charcoal.

Method (A): Reductions in methanol.

Initially, the reduction method used by Coutts and Edward, 1966 was followed except that methanol was used as solvent instead of an ethanol-methanol mixture. The same products were isolated, i.e. the major amphoteric compounds which were claimed to be the 9-hydroxypyrazolo[3,4-b]quinolines (99 a-c), and the minor ones which Coutts and Edwards (1966) left unidentified. However, due to some difficulties in obtaining pure analytical samples of some of these derivatives, a modification in the reduction procedure was sought.

Method (B): Reductions in 10% sodium hydroxide solution.

The O-nitrobenzylidene derivatives (318a-c) were first reduced by means of sodium borohydride in dioxane solution. This resulted only in the reduction of the benzylidene double bond and 4-(2-nitrobenzyl)-2-pyrazolin-5-ones (319) were isolated in excellent yields.

(319) [CH form]   (319) [OH form]
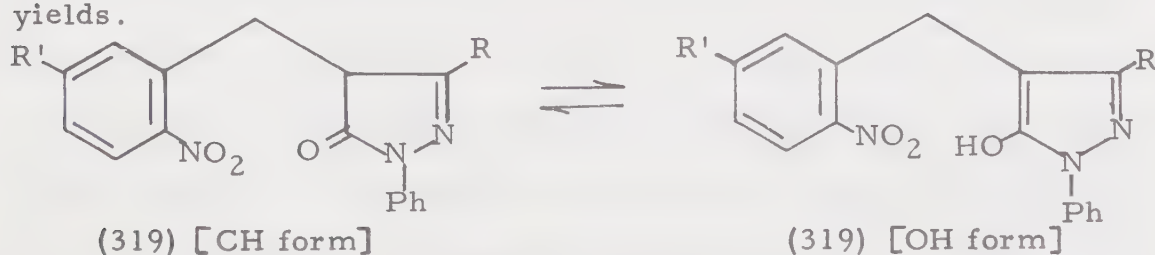
a; R = CH$_3$,   R' = H

b; R = Ph,   R' = H

c; R = CH$_3$,   R' = Cl

Once the benzylidene double bond is reduced, these pyrazolones (319) become soluble in dilute alkali due to their ability to enolize. In view of this, catalytic (10% Pd-C) sodium borohydride reductions of the pyrazolones (319) were carried out in dilute sodium hydroxide solution. Acidification of the filtrate from the reaction with dilute acetic acid caused precipitation of the reduced products.

By using this modified procedure, only one type of product was isolated. Although melting points were considerably higher than those of the amphoteric products obtained by reduction in methanol, they had the same solubility characteristics and the same i.r. spectra as those reported for the compounds prepared by Coutts and Edwards (1966).

Narang et al (1934) concluded that the 9-hydroxypyrazolo-quinoline (99 a) was the reduction product of the pyrazolone (98 a) from a correct elemental analysis, and because the product was found to be soluble in both acids and alkalies. When Coutts and Edwards (1966) reduced the same compound (98 a) and derivatives (98 b-g), they concluded that in addition to the correct elemental analyses and solubility characteristics, the i.r. spectra of the reduction products were also in agreement with structure (99). The i.r. spectra(solid) showed broad absorption in the 2100-3500 cm^{-1} range with maxima between 2850 and 3090 cm^{-1} which was attributed to the N-OH function. Also a C$=$O absorption band was apparently absent from these spectra. Similar spectra were obtained when the pure samples obtained in the present investigation were examined as solids (KBr or nujol), but two additional medium size absorption maxima were located at ~3200 and ~3350 cm^{-1}. This was initially considered to be due to the ability of

such compounds (99) to tautomerise (320) and thus display an NH

absorption band in addition to that of the N-OH function.   However, the

(99)   (320)

plausibility of N-hydroxy structures (99) being formed at all, was

seriously questioned when the n.m.r. and mass spectra of these

reduction products were recorded and interpreted.

The n.m.r. spectrum (in DMSO-d_6) of the amphoteric

product obtained by reduction of the pyrazolone (319a), displayed two

signals at $\delta 2.1$ (CH_3) and at $\delta 3.43$ (CH_2) and an aromatic multiplet

(12 protons).   When the sample was shaken with deuterium oxide,

three protons within the aromatic area were found to be D-exchange-

able.   Three D-exchangeable protons, with almost the same chemical

shifts were also found in the n.m.r. spectrum of the reduction

product of the phenyl analog (319b).   These three protons shifted

upfield when $CDCl_3$ was the solvent used;   in this solvent they appeared

as a broad peak around $\delta 6.0$.   The presence of three D-exchangeable

protons in each of these spectra does not agree with the proposed

structures (99 $\rightleftharpoons$ 320) in which only one or two such protons would be

expected.

The mass spectra of the reduction products (Fig. 1) dis-

played molecular ions consistent with the molecular formulae of the

proposed structures (99 a,b).   However, the mode of fragmentation

of these compounds under electron impact (Scheme 2) revealed that

intact pyrazolone ring   (ion b) was still present in the molecules.

The expulsion of an oxygen atom or an ȮH radical which might be expected from a cyclic N-hydroxy structure (99) was not demonstrated. Both of these losses were displayed by some authentic N-hydroxy compounds prepared and described later in this thesis. Instead, the expulsion of a molecule of water (to form ion $\underline{d}$ or $\underline{e}$) followed by the loss of a hydrogen atom (presumably to form the stable pyrazolo-quinoline $\underline{f}$) was observed (see Scheme 2). The absence of an $(M-18)^+$ ion in the mass spectrum of the related amine (416), in which the methylene group is replaced with a sulfur atom, suggested that one of the methylene hydrogen atoms is involved in the loss of a water molecule from the molecular ion of (321). This suggestion was also supported by the presence of an $(M-18)^+$ ion in the mass spectrum of the triacetylated derivative (326) (see Scheme 4, p. 94).

At this point, it was concluded that the proposed structures (99 $\rightleftharpoons$ 320) for the reduction products in question were not correct. The isomeric amine structure (321) was seen to fit all the previously described data. Such a structure is best written in its three possible

(321) [CH form]   Ph

(321) [OH form]   Ph

(321) [NH form]   Ph
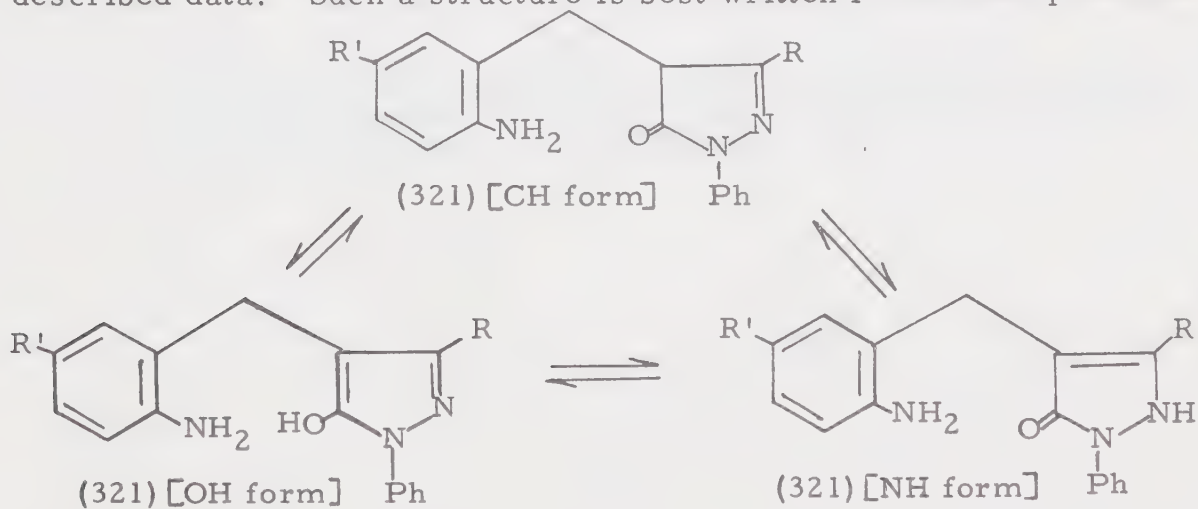
a; R = CH$_3$,   R' = H

b; R = Ph,   R' = H

c; R = CH$_3$,   R' = Cl
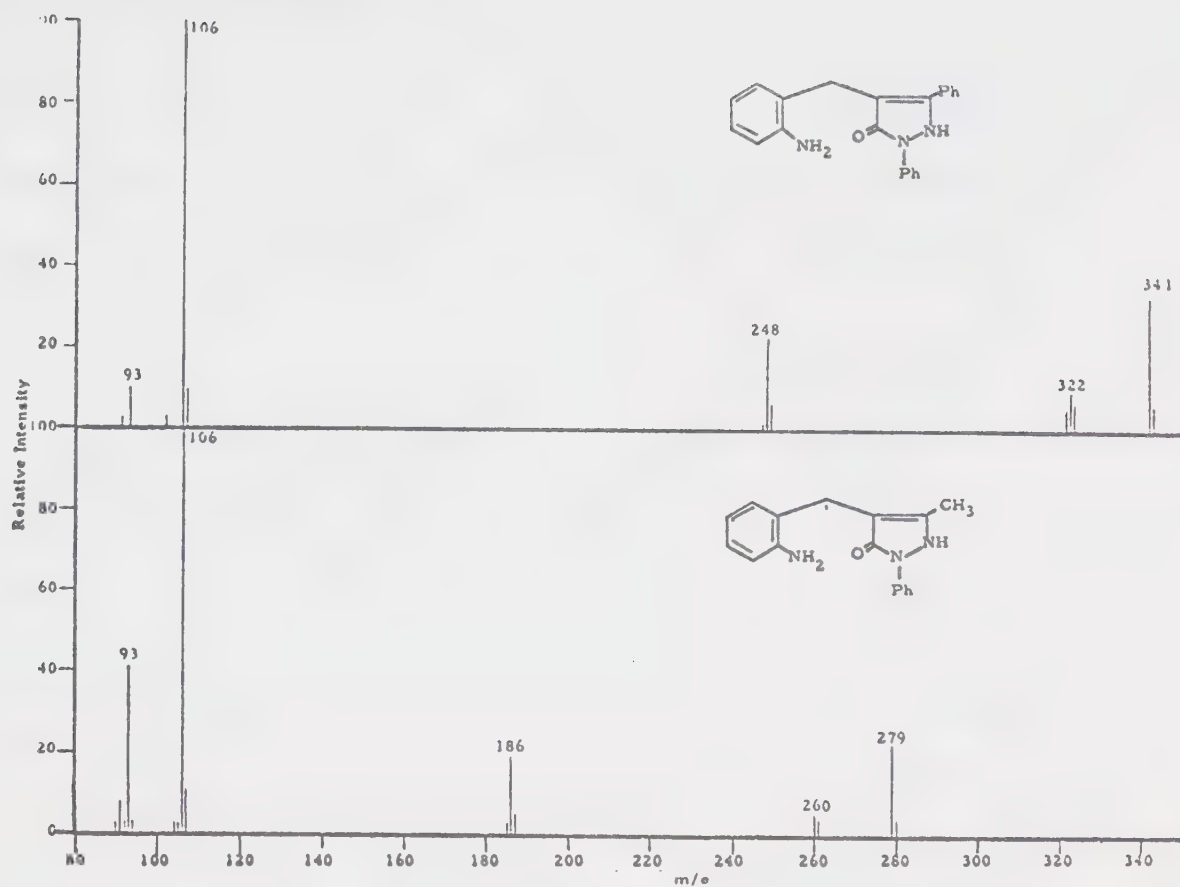
Fig. 1: Portions of the mass spectra of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a) and 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b).

tautomeric forms which can be designated, using the nomenclature of Katritzky and Maine (1964) as the CH, NH or OH forms according to the position of the labile proton.
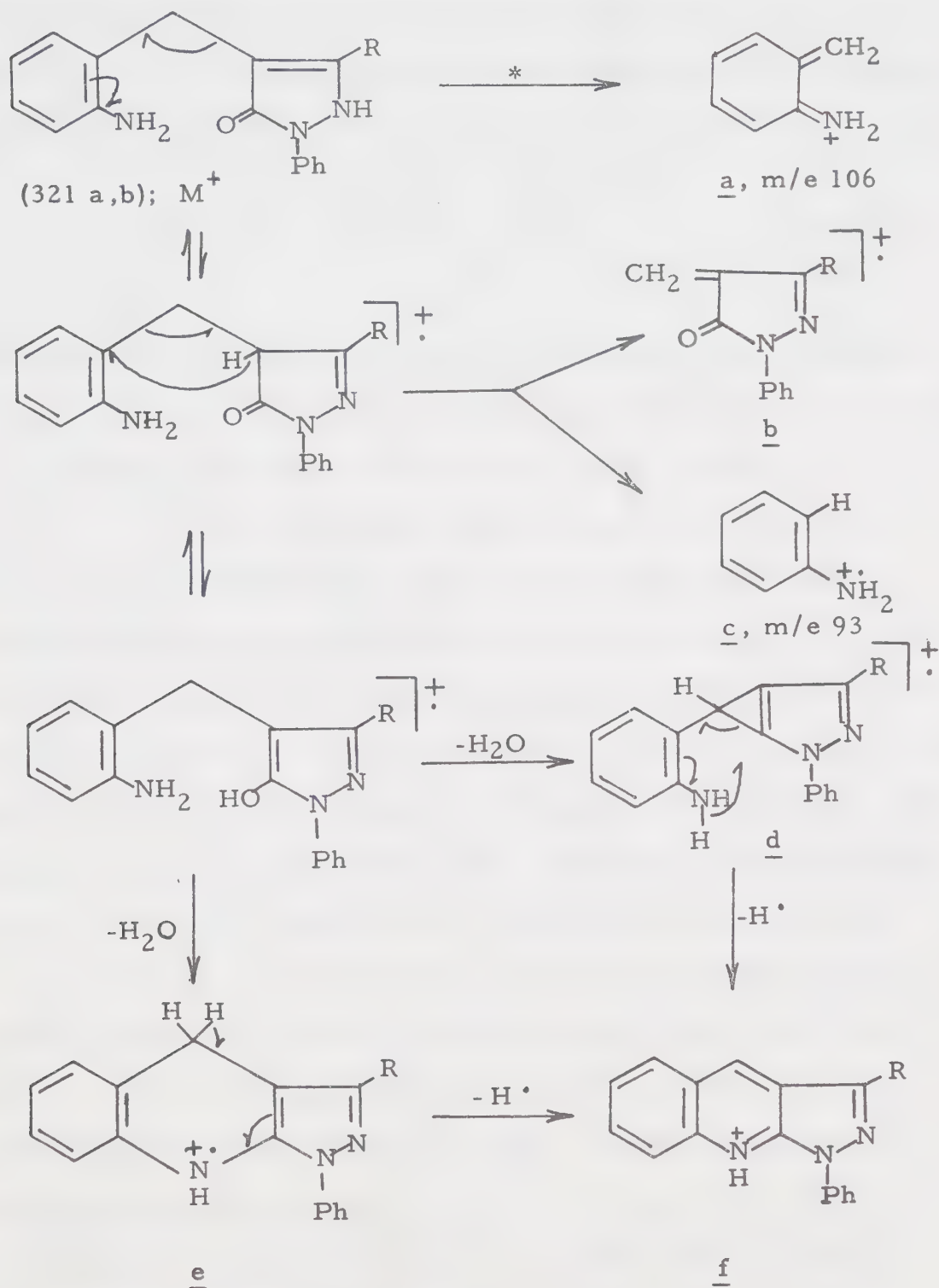
Scheme 2

Two main reasons contributed to the earlier incorrect assignment of structure (99) to the amphoteric reduction products. The first was their solubility in dilute alkali solutions which was believed to be due to the acidity of the N-hydroxy function. It is true that some cyclic hydroxylamines such as (255) (Kato and Yamanaka, 1965) and (7, R=Ph) (Sundberg, 1965) are soluble in alkalies. How-

(255)　　　　　　　　　　(7)　　　　　　　　　　(322)
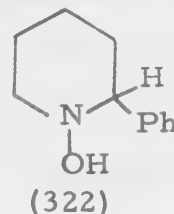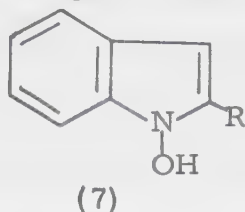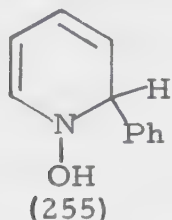
ever, some other related compounds such as (7, R=CH$_3$) (Acheson et al, 1970) and (322) (Kato and Yamanaka, 1965) are known to be only very weakly acidic and do not dissolve in alkali solutions.

The second reason which is probably more important, was the fact that C═O absorption was apparently absent from the i.r. spectra of the reduction products when solids were examined. This was taken as an indication that cyclization involving the lactam C═O groups had occurred. It is now revealed that C═O absorption can be demonstrated in both solution and solid spectra of the reduced compounds. Dilute solutions (2%) of the amines (321a,b) in chloroform, gave spectra which displayed a C═O absorption band at 1712 cm^{-1} for (321a) and at 1711 cm^{-1} for (321b). This indicated that the amines existed mainly in the CH form in chloroform (Newman and Pauwels, 1969). These bands completely disappeared when the more polar dimethylsulfoxide was used as a solvent. Instead, another C═O absorption doublet was present at 1660 cm^{-1} (average) for (321a) and at 1654 cm^{-1} (average) for (321b). This shift in the carbonyl absorption is expected when the NH form is present since the

pyrazolone ring is comparable to an α,β-unsaturated ketone in this tautomer (Nakanishi, 1962). The multiplicity of these bands and their occurrence at lower frequencies than expected are considered to be due to hydrogen bonding with solvent. The presence of the OH form, in addition to the NH form, in dimethylsulfoxide was indicated mainly by the $C=N$ absorption bands around 1603 cm^{-1}.

A closer look at the i.r. spectra of these amines (321) in the solid form, revealed the presence of a strong absorption band at 1628 cm^{-1} in (321a) and at 1625 cm^{-1} in (321b). The possibility of these bands being due to a $C=O$ absorption was not considered initially and they were assigned to $C=N$ absorption. However, the absence of similar bands in the spectra of intermediate pyrazolones (319) and their presence in those of some amine derivatives e.g. (324) which should be devoid of a $C=N$ double bond, suggested that these bands might be due to a bonded $C=O$ absorption. To examine this possibility, the i.r. spectra of the pyrazolones (317) and (319) were recorded in the solid form. In agreement with some of the earlier reports* (Pelz et al, 1960; Refn, 1961), 3-methyl-2-phenyl-1-pyrazolin-5-one (317a) and 1,3-diphenyl-2-pyrazoline-5-one (317b) were found to exist only in the OH-forms in the solid state. The lack of any $C=O$

(317) ⌈CH form⌉   (317) [NH form]   (317) [OH form]

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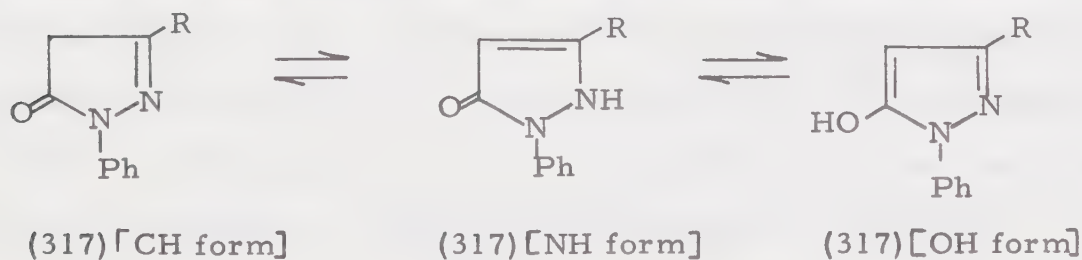
* Katritzky and Maine (1964) considered that, except in special cases, all pyrazolones including (317a) and (317b) exist in the solid state as strongly bonded NH-form which are capable of proton transfer to give the OH-form.

absorption confirms the absence of any contribution from the CH or NH-forms. The $C = N$ absorption bands in the spectra were located at 1606 cm^{-1} in (317a) and at 1601 cm^{-1} in (317b). The two 4-(2-nitro-benzyl)-2-pyrazolin-5-ones (319a,b) were also found to exist in OH forms in the solid state. Their spectra displayed broad OH absorption bands between 2400 and 3200 cm^{-1} and $C = N$ absorption was assigned to the bands at 1605 and 1604 for (319a) and (319b) respectively; no other absorption was demonstrated in the 1600-1800 cm^{-1} region.

In the spectra of the amines (321), the absorption bands at 1604 for (321a) and 1600 for (321b) could be assigned to the $C = N$ absorption in agreement with the nitro analogs (321a) and (321b). Accordingly, the other strong absorption bands at 1628 and 1625 cm^{-1} in (321a) and (321b) respectively must be due to a bonded $C = O$ absorption. This could be due to the contribution of the NH tautomer in addition to the OH tautomer in the solid state. In the NH tautomer, the $C = O$ absorption is expected to be around 1670 cm^{-1}, but this could be shifted to a lower frequency due to the presence of a strong inter-molecular or intramolecular hydrogen bonding. The possibility of the latter was indicated by the presence of the amine absorption maxima at unusually low wave numbers [3200 and 3345 cm^{-1} for (321a) and 3170 and 3350 for (321b)]. A case in which a lactam $C = O$ group was found to absorb at such a low frequency was reported by Newman and Pauwels (1969). In the pyrazolone (323) a band found at 1620 cm^{-1} was assigned to the intramolecularly hydrogen bonded lactam $C = O$ group.

(323)
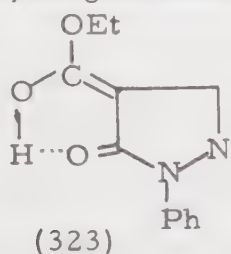
The assignment of the absorption band around 1625 cm^{-1} in (321) to a C$=$O absorption was substantiated by examining the i.r. spectra of some of the derivatives of the amine (321). When the mono-methylated derivatives (324) were prepared (see later), two strong absorption bands were located at 1624 and 1630 cm^{-1} in the solid spectra of compounds (324a) and (324b) respectively. In these struc-tures no tautomerism is possible and accordingly a C$=$N absorption should not be present; only C$=$O absorption is expected which must

(324)
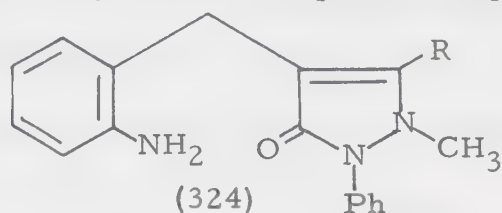
a, R = CH$_3$

b, R = Ph

be the origin of these bands mentioned above.

On the other hand, the dibenzoyl derivative (325) and the

(325)

(326)
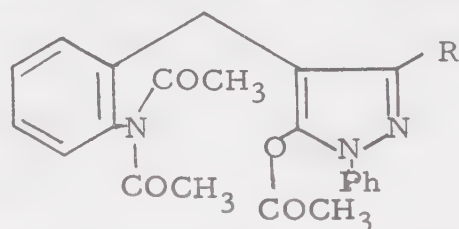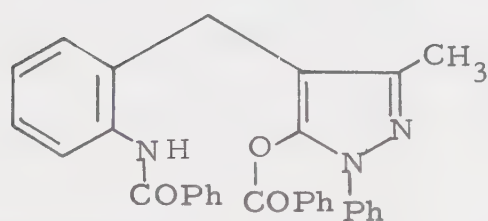
a, R = CH$_3$

b, R = Ph

triacetyl derivatives (326) will show C$=$N absorption bands. These bands were found at 1600 cm^{-1} in the dibenzoyl derivatives (325) and at 1600 and 1595 cm^{-1} in the triacetyl derivatives (326a) and (326b) respectively, and apart from the acyl C$=$O absorptions, no other bands were present in the 1600-1800 cm^{-1} region.

This, added to the above discussion, provides conclusive evidence that the strong absorption bands present around 1625 cm^{-1}

in the i.r. spectra of the solid amines (321) are actually due to a strongly bonded lactam $C{=}O$ absorption. Accordingly, these amines are best represented by both the NH and OH forms, rather than by the CH form.

Some derivatives of 4-(2-aminobenzyl)-2-pyrazolin-5-ones (321a,b):

Methyl derivatives (324) of the amines (321a, 321b) were prepared by reacting them with dimethylsulfate. N-Methyl derivatives (324) were the only products obtained although theoretically, two other isomers (327 and 328) were possible. Evidence in support of the N-methyl structure was the presence of a three-proton signal at

(324)

(327)   a, R = CH$_3$ (328)

b, R = Ph
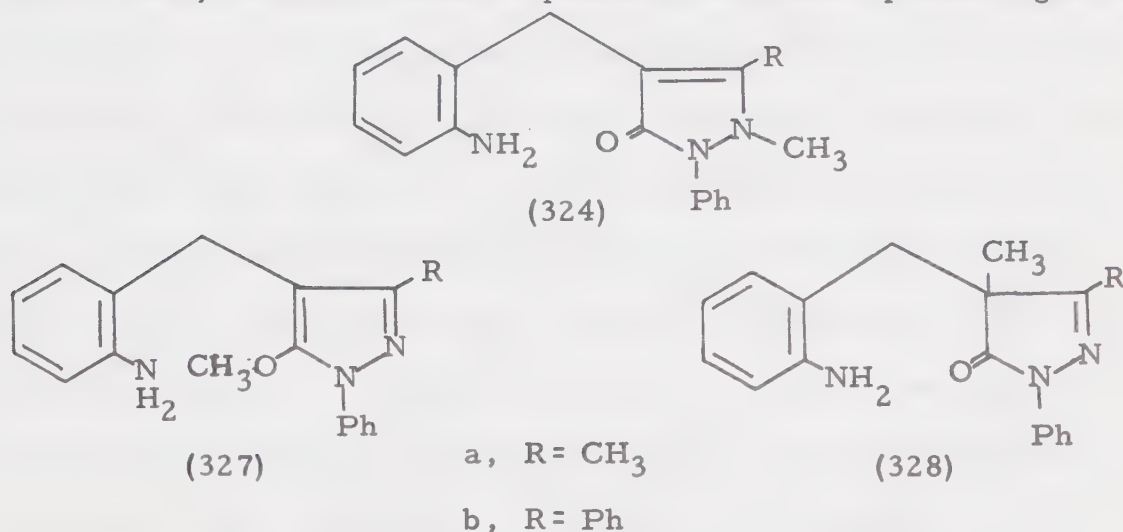
δ2.98 in the n.m.r. spectrum of the methylation product from (321a) and a similar signal at δ2.91 in the product from (321b). This chemical shift is similar to that of the N-methyl signal of antipyrine (329) and aminopyrine (330) which come to resonance at δ2.95 and

(329)   (330)
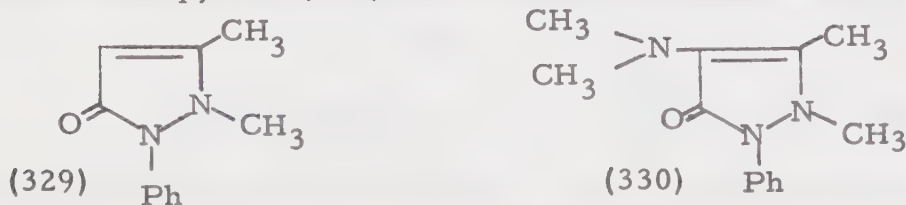
2.90 respectively. Methylation at C-4 was ruled out by the absence of a $C{=}O$ absorption band near 1720 cm^{-1} (Katritzky and Maine, 1964)

in the spectra of both methylated derivatives. These results are in

agreement with the fact that it is easier to methylate at the N-2 rather

than at the C-4 position of the pyrazolone ring (Wiley and Wiley, 1964).

Methylation of 3-methyl-1-phenyl-2-pyrazolin-5-one(317a) is known

(Bodendorf and Raaf, 1955) to occur at N-2 when dimethyl sulfate is

used as an alkylating agent. When the pyrazolone (317a) was treated

with dimethyl sulfate under the same conditions used to prepare (324),

only N-methylation occurred and antipyrene (329) was the single product

isolated.

Additional evidence to confirm the presence of the N-methyl

function in the methylation products was obtained from an examination

of the mass spectra of both compounds. Molecular ions of m/e 293

and m/e 355 were present in the spectra of (324a) and (324b) respec-

tively. The methyl derivative (324 a) displayed a strong fragment

ion (97% of the base peak) at m/e 56 which corresponds to

$CH_3-C\equiv\overset{+}{N}-CH_3 \longleftrightarrow CH_3-\overset{+}{C}=N-CH_3$. This fragment was also

the base peak in aminopyrine (330) and in the pyrazolone (408) which

is described later in this study. Similarly, the strongest ion in the

mass spectrum of the phenyl analog (324b) was at m/e 118 which

corresponds to $C_6H_5-C\equiv\overset{+}{N}-CH_3 \longleftrightarrow C_6H_5-\overset{+}{C}=N-CH_3$.

(408)
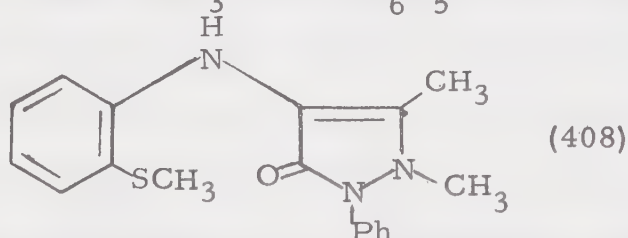
A relatively strong (M-30) fragment ion was observed in

the spectra of both (324a) and (324b). An accurate mass measure-

ment of this ion (m/e 325) in compound (324b) identified it as

$C_{22}H_{17}N_2O$ and showed that it was formed by the expulsion of CH_4N

from the molecular ion. A metastable of m/e 297.55 suggested a
direct fragmentation, $C_{23}H_{17}N_3O - CH_4N \longrightarrow C_{22}H_{17}N_2O$ and
supported the previous conclusion that an N-methyl group was present
in (324b).

- - -

The action of benzoyl chloride on the amine (321 a) pro-
duced a dibenzoyl derivative identified as (325) from its elemental
analysis $(C_{31}H_{25}N_3O_3)$, i.r., n.m.r., and mass spectra. The i.r.

(325)
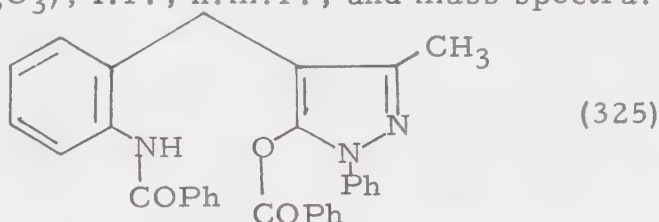
spectrum (solid) (325) displayed two C$=$O absorption bands at 1645
cm^{-1} (NHCOPh) and at 1760 cm^{-1} (OCOPh) and an NH absorption band
at 3315 cm^{-1}. The n.m.r. spectrum (CDCl$_3$) showed a methyl signal
at $\delta 2.12$, a methylene signal at $\delta 3.8$, an aromatic multiplet between
$\delta 6.8$ and 7.9 (19 protons) and a D-exchangeable proton at $\delta 8.0$ (NH).

This compound was insoluble in sodium hydroxide which
indicated that the labile proton in the pyrazolone ring was replaced
during benzoylation. A carbonyl stretching frequency of 1760 cm^{-1}
supports the proposed ester structure (325). Also, in the mass
spectrum of (325), the molecular ion was at m/e 487, and fragmented
initially by the expulsion of benzoyl (PhCȮ) and benzoyloxy (PhCOȮ)
radicals and a benzoic acid molecule. The presence of two strong
metastables at m/e 275.06 and 273.65 respectively suggested that the
last two expulsions were direct fragmentations of the molecular ion.

Acetylation of the amine derivatives (321a and 321b) by heating with acetic anhydride for one hour gave monoacetyl derivatives. However, when heating was prolonged, triacetyl products were isolated. These were identified as 4-(2-acetylaminobenzyl)-1-phenyl-2-pyrazolin-5-ones (332) and 5-acetyloxy-4-(2-diacetylaminobenzyl)-1-phenylpyrazoles (326) respectively.

(332) (326)
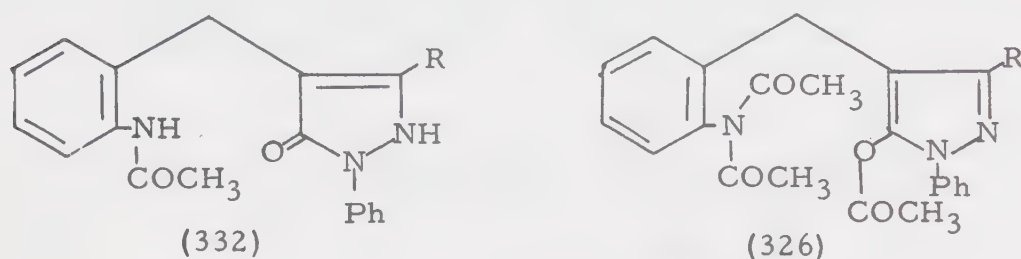
a, R = CH$_3$

b, R = Ph

Due to their ability to enolize, the monoacetylated derivatives (332) were soluble in dilute alkali solutions. They analyzed correctly for $C_{19}H_{19}N_3O_2$ (332a) and $C_{24}H_{21}N_3O_2$ (332b) and the i.r. spectrum of each displayed two C=O absorption bands attributable to the amide and lactam functions. The mass spectrum (Fig. 2) of (332a) had a molecular ion at m/e 321 which fragmented initially by the expulsion of a water molecule, a ketene molecule and a CH_3CONH radical to give ions a, b and c respectively. The fragmentation pathways and some of the fragment ions formed in the spectrum of this compound are tentatively identified in Scheme 3.
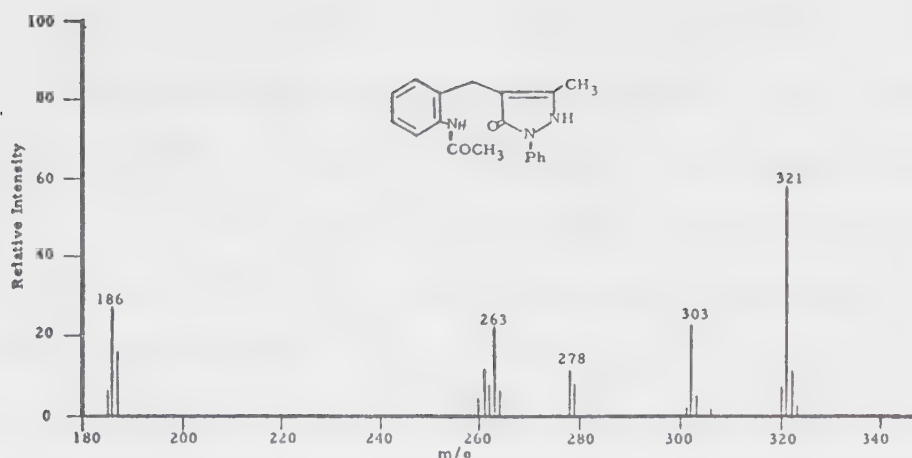
Fig. 2: A portion of the mass spectrum of 4-(2-acetylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (332a).
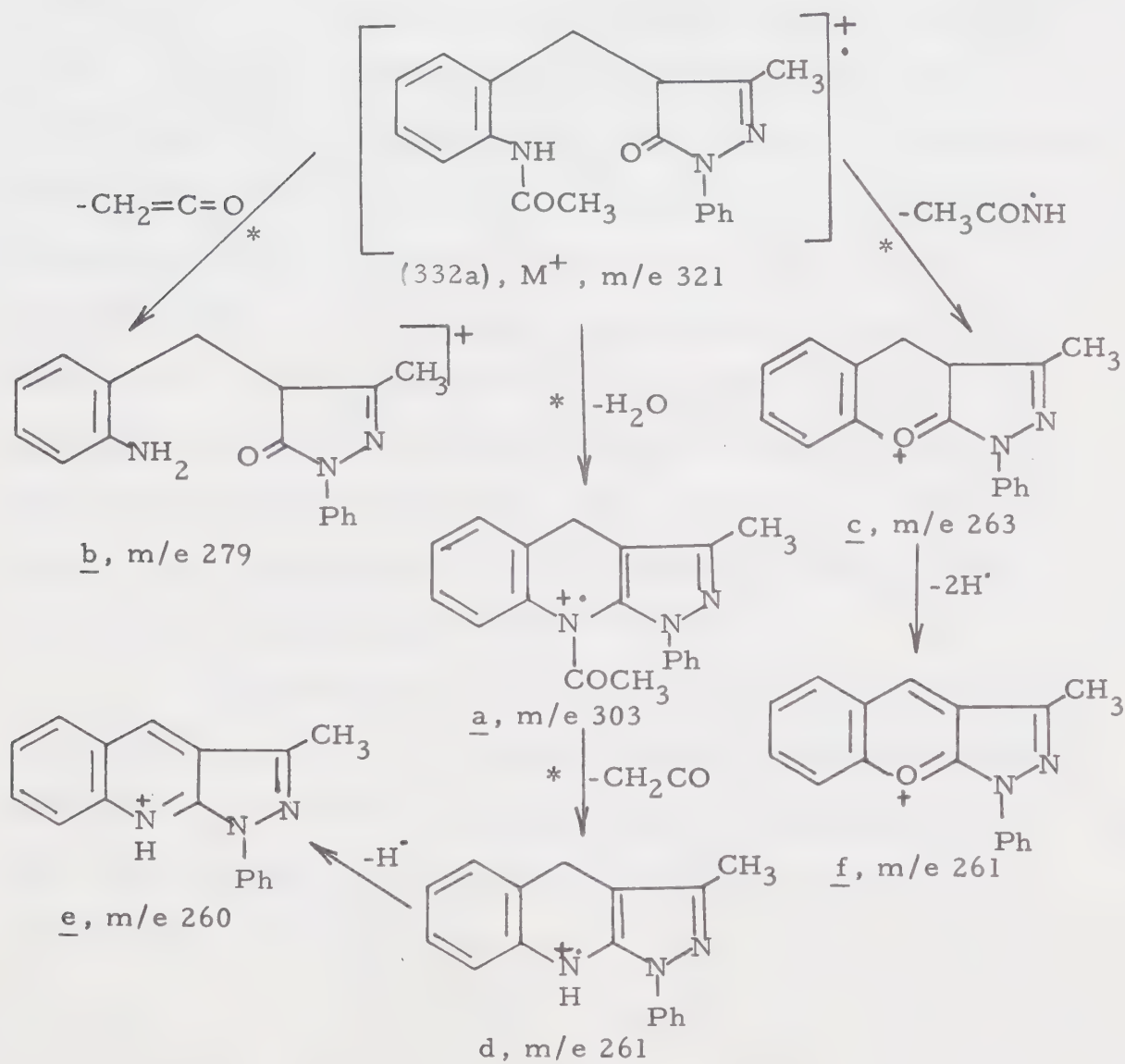
Scheme 3

Both triacetyl derivatives (326) dissolve slowly in dilute alkalis. When the alkaline solutions were acidified, they yielded the monoacetyl derivatives (332). The elemental analyses as well as the i.r., n.m.r., and mass spectra supported the proposed structures (326a and 326b). Both n.m.r. spectra displayed a six-proton signal for the N-diacetyl function, a three-proton signal for the O-acetyl group, a methylene signal and an aromatic multiplet. The i.r. spectra was devoid of any NH or OH absorption bands. The methyl derivative (326a) displayed three strong $C≡O$ bands at 1790 cm^{-1} ($OCOCH_3$), and at 1685 and 1730 cm^{-1} due to the N,N-diacetyl doublet (Grove et al, 1956). In the i.r. spectrum of the phenyl analog (326b), the corresponding bands appeared at 1793, 1705 and 1718 cm^{-1}. The presence of the carbonyl absorptions of the N,N-diacetyl function at a higher frequency than the carbonyl absorption bands of the monoacetyl compounds (332) has already been commented upon (Abramovitch, 1957). However, the ester carbonyl absorption near 1790 cm^{-1} is unexpected and should be contrasted with the values of 1770 cm^{-1} for phenyl acetate (Witkop and Patrick, 1952; Grove et al, 1956). The reason may be the presence of bulky substituents in the o-position (c.f. Schubert and Saveeney, 1955).

The triacetylated derivative (326a) fragmented mainly by successive expulsions of two ketene molecules to yield the molecular ion of the mono-acetylated compound (332a). The (M-42)$^+$ ion (a) also expelled a water molecule to give a relatively strong ion of m/e 345 (Fig. 3, Scheme 4).
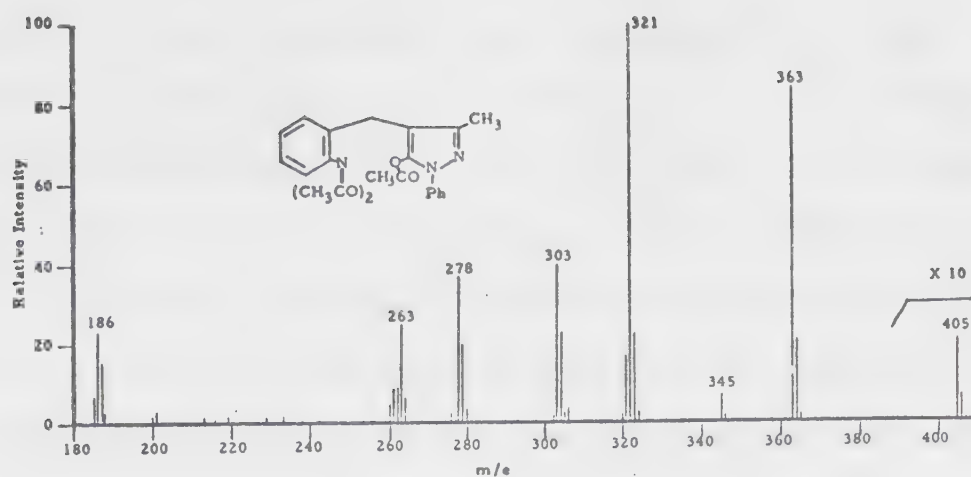
Fig. 3: A portion of the mass spectrum of 5-acetyloxy-4-(2-diacetyl-aminobenzyl)-3-methyl-1-phenylpyrazole (326a).
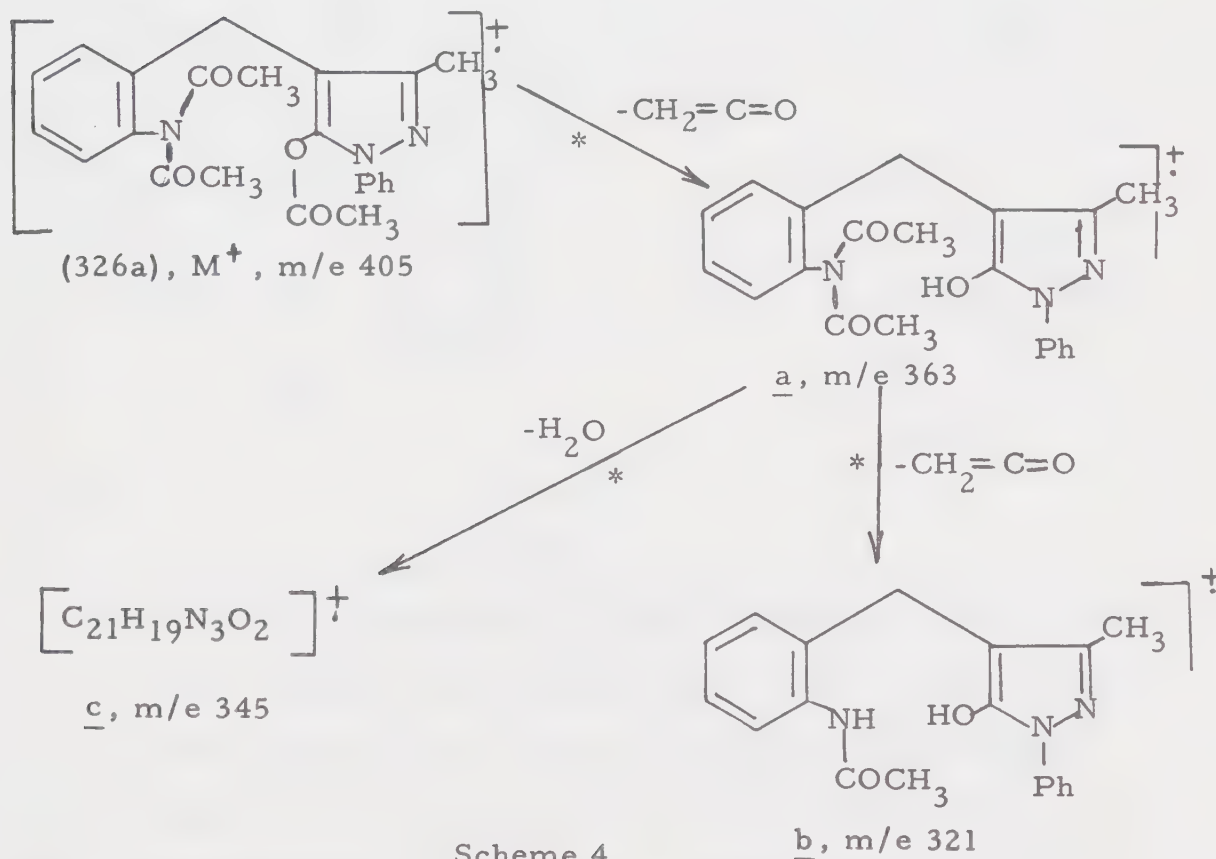
Scheme 4

Attempts were made to prepare the O-acetyl derivatives

(335) through the reduction of the 5-acetyloxy-4-(2-nitrobenzyl)-1-

phenylpyrazoles (334). The latter compounds were prepared by treat-

ing the nitropyrazolones (333) with acetic anhydride. The presence of

O-acetyl functions in the products was confirmed by i.r. spectroscopy

(1781 cm^{-1} in 334a and 1790 cm^{-1} in 334b), by n.m.r. (O-CO$\underline{C}$H$_3$

protons came to resonance at δ 2.03 in 334a and δ 2.02 in 334b) and

by mass spectral fragmentation (direct loss of CH$_3$COO$^{\bullet}$ radical from

the molecular ion). When the O-acetyl compounds (334) were reduced

either by catalytic hydrogenation over platinum or by sodium boro-

hydride/palladium-charcoal in dioxane, oily products were obtained.

a, R = CH$_3$

b, R = Ph
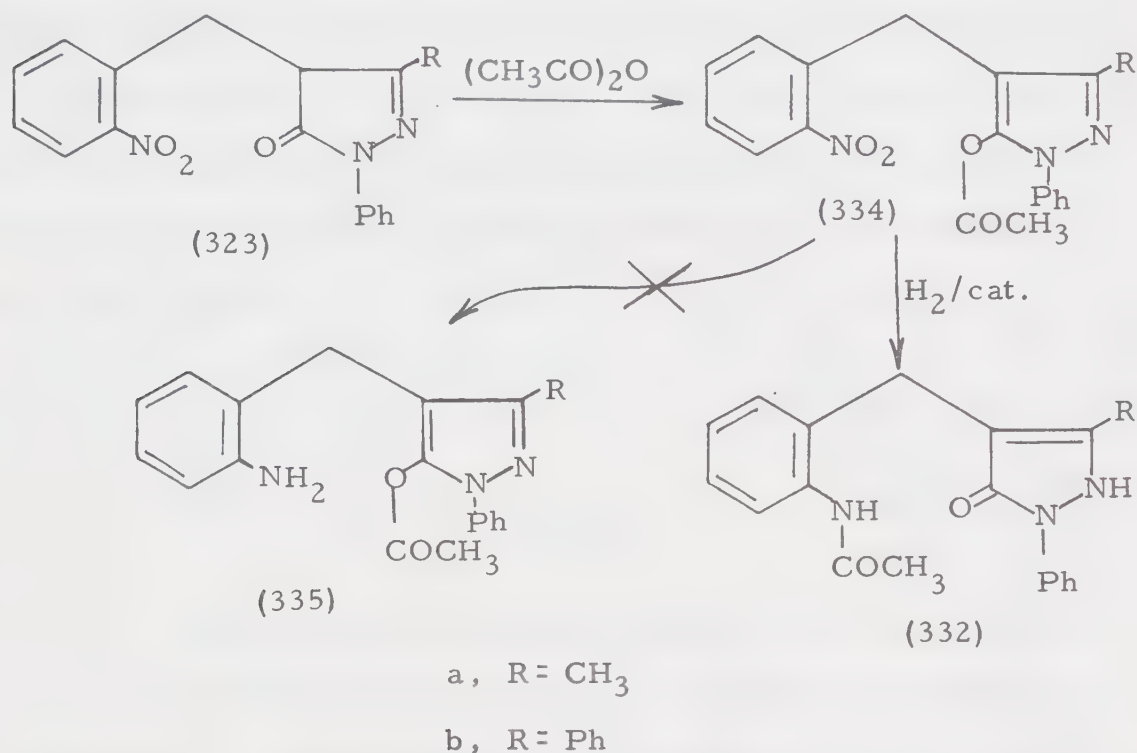
The only crystallizable compounds isolated were the N-acetyl deriva-

tives (332) rather than the desired O-acetyl derivatives (335). Identi-

fication of these compounds was done by comparison with authentic

samples prepared and described earlier. The isolation of such

products indicated that the acetyl group, originally attached to the

oxygen atom of the pyrazole ring, migrated to the amine function

once the latter was formed. Such migration of acyl residues from

oxygen to nitrogen (O⟶N) or _vice_ _versa_ (N⟶O) is a common

phenomenon which occurs, for example, with all α-amino-β-hydroxy

compounds in the aromatic, hydroaromatic and aliphatic series

(Witkop and Patrick, 1952). Examples of 1,3-acyl migrations have

also been demonstrated (Miller, 1965) and examples of acyl migrations

involving different pairs of heteroatoms are known and have recently

been reviewed by Akabori (1965) and by Pavlova and Rachiniskii (1968).

Also, Tani et al (1964), reported some acyl exchange reactions between

N-acyl lactams and amines, but no examples comparable to the one

shown in this present study between the O-acetyl lactam and the amine

function seem to have been reported. In this instance, the amine and

acetyl group seem suitably orientated to allow this migration to occur

intramolecularly (Scheme 5) although an intermolecular migration

cannot be ruled out.

Scheme 5

(332)
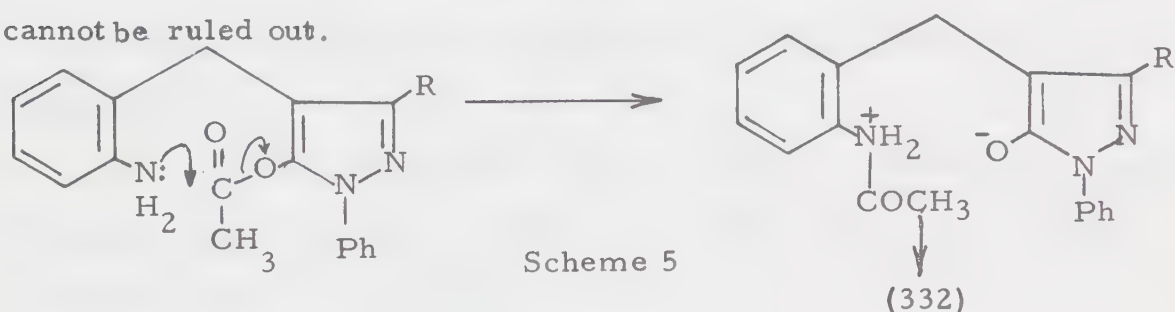
The final piece of evidence sought in order to confirm the

amine structure (321) was to attempt a preparation of Schiff bases

(336) through the condensation of these amines with some aldehydes

and ketones. However, Schiff bases were not isolated. Instead,

the products cyclized to spiro-tetrahydroquinoline derivatives (337),

(336)

(337)
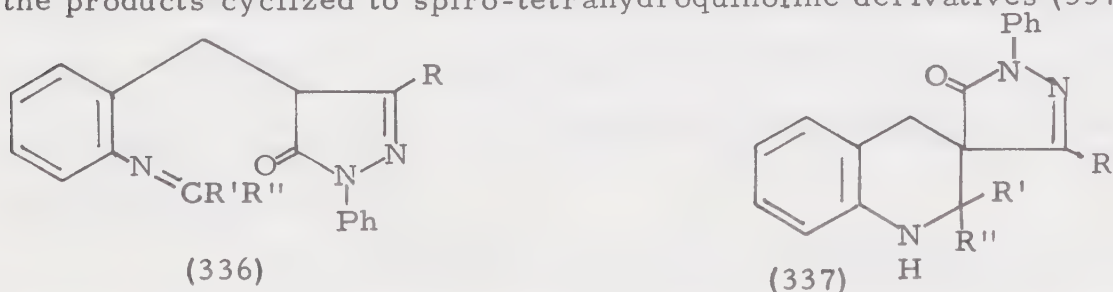
the formation and identity of which will be discussed in detail in a

later section.

Method (C):   Reductions in dioxane.

It is well known that metal hydride reductions are often in-
fluenced by the nature of the solvent used (Brown, 1962; Coutts, 1969).
This fact led to a repeat of the sodium borohydride/palladium-charcoal
reductions just described, in another solvent to determine whether this
might facilitate cyclization to the desired N-hydroxy compounds.
Coutts and his co-workers (Coutts and Wibberley, 1963; Coutts and
Hindmarch, 1966) found dioxane to be a suitable solvent for their cataly-
tic sodium borohydride reductions.   This solvent was also used for the
reduction of some 4-(2-nitrobenzylidine)-2-pyrazolin-5-ones (98) but
the reduction products were left unidentified (Coutts and Edwards, 1966).
i)   Reduction of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-
5-one (318a).

This reduction was repeated with some modification to the
literature method (Coutts and Edwards, 1966).   When hydrochloric
acid was used to decompose the surplus hydride and precipitate the
acidic products, a yellow impure solid was obtained.   Replacing hydro-
chloric acid with acetic acid produced a white solid which was easily
purified by fractional crystallization to yield three compounds.   The
major product was identified as the cyclic N-hydroxy compound, spiro-
[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5-one)]
(338).   The other two products were spiro[(indoline-2,4'-(3'-methyl-
1'-phenyl-1H-pyrazolin-5'-one)](339) and the previously described
amphoteric amine (321a).

The identity of the N-hydroxy compound (338) was based
initially on the observations that it reduced Tollen's reagent and that
it analyzed correctly for $C_{17}H_{15}N_3O_2$, a formula verified by the

(318a) → (338) + (321a) + (339)

NaBH$_4$/Pd-C, Dioxane
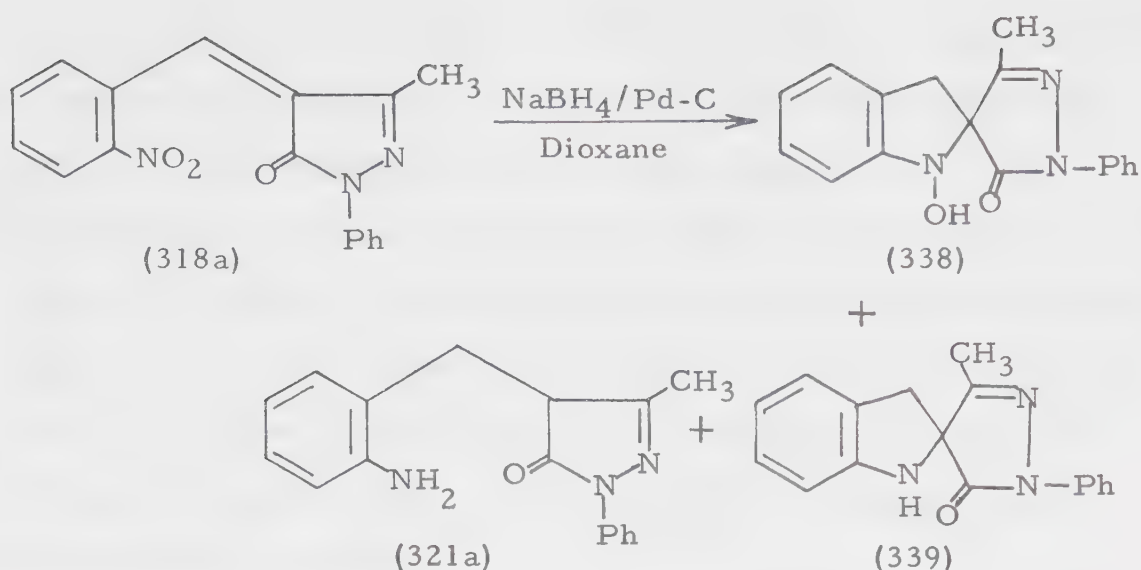
presence of a molecular ion at m/e 293 in its mass spectrum. In the

presence of alkali, this compound gave a purple-red color with tri-

phenyltetrazolium chloride, a reaction which is claimed to be specific

for hydroxylamine derivatives (Snow, 1954; Rogers, 1955). That the

pyrazolone ring still remained intact was clear from the i.r. spectrum

which showed a C=O absorption band at 1690 cm^{-1}. This C=O is

present at a lower frequency than that usually demonstrated in 5,5-

disubstituted pyrazolone derivatives. However, an intramolecular

hydrogen bonding with the N—OH groups is possible in such a structure

(338) in which the donor and the acceptor groups are in peri position.

Katritzky and Logowski (1971c) described a similar effect in 8-hydroxy-

quinoline-1-oxide and its azo derivative (340). Support for hydrogen-

(338)   (340)
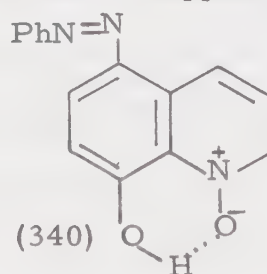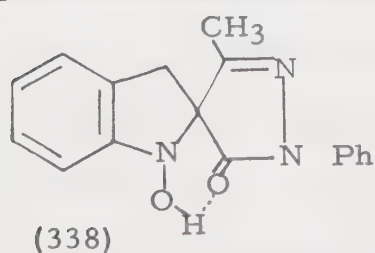
bonding in (338) is the position of the i.r. O—H stretching band which

was broad and of low frequency centered at 3275 cm^{-1}.

Another argument in favor of the cyclic structure (338) was the lack of solubility of this compound in dilute alkalis, a property shown by all pyrazolones having a hydrogen atom at C-4. This cyclization was not unexpected since the hydrogen atom at C-4 is known to be very reactive; it undergoes the characteristic condensation and substitution reactions of an active methylene group (Wiley and Wiley, 1964). Once the C-4 position is disubstituted, the acidity of the pyrazolone ring becomes so weak that it is now essentially neutral (Wiley and Wiley, 1964).

The n.m.r. spectrum of this compound (in DMSO-d_6) displayed a methyl signal at δ3.28, a slightly broad methylene signal at δ3.28, and a one-proton signal at δ9.67 which exchanged with deuterium. Assignment of this D-exchangeable signal to the N—OH function is consistent with some earlier reports (Kato and Yamanaka, 1965; Acheson et al, 1970; Schweizer and Kopay, 1972). The appearance of the two methylene protons as a broad singlet was not expected since these two protons are non-equivalent. However, this appears to be only a solvent effect since the n.m.r. spectrum repeated in pyridine displayed, for these methylene protons, a doublet of doublets with a geminal coupling constant of 16 Hz. Also, in pyridine, the N—OH signal appeared further downfield as a broad peak centered at δ12.1.

Initially, two other isomeric structures(315 and 341) were considered along with the N-hydroxy structure (338) for the major reduction product of (318a). The hydroxylamine structure (315) suggested by Pound (1970), was only a remote possibility since the benzylidine double bond would be reduced under the reduction conditions used. The sodium borohydride reduction of this double bond

with dioxane as a solvent was demonstrated earlier. The presence of
only one D-exchangeable proton and a methylene signal in the n.m.r.
spectrum of this product completely ruled out the hydroxylamine
formula (315). The isomeric structure (341) was a more serious

(315)   (341)
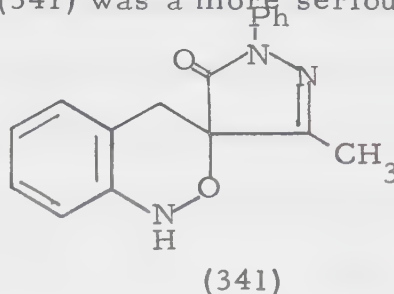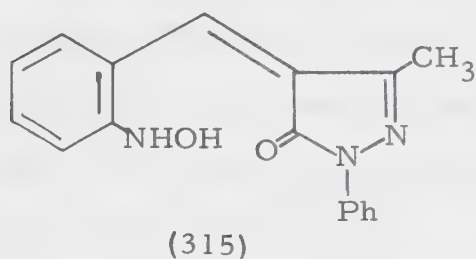
possibility due to the fact that it is compatible with some of the i.r.
and n.m.r. spectral data. However, the fact that the product isolated
was neutral suggested that such a structure is not appropriate. Com-
pound (341) is expected to be basic because it is known that the related
isoxazolidines (cyclic 5-membered-NH-O-compounds) are strong
bases (Quilico, 1962).

The mass spectral fragmentatation pattern of the product
$C_{17}H_{15}N_3O_2$ was very helpful in confirming the appropriateness of the
cyclic N-hydroxy structure (338). As will be discussed in detail
later, the expulsion of an oxygen atom and a water molecule as well
as the direct loss of an ȮH radical from the molecular ion were of
special diagnostic value. Also, the chemical reactivity of this
compound (including reduction, oxidation, acylations, sulfonation and
reactions with nucleophiles) proved beyond any doubt that the N-hydroxy
structure (338) was correctly assigned.

- - -

The minor products of the reduction of the pyrazolone
(318a) were identified as the amine (321a) and the indoline (339). The

former was identified by comparing its spectral properties with those reported earlier. The indoline (339) was identified by its elemental analysis $(C_{17}H_{15}N_3O)$, its mass spectrum (M^+ at m/e 277) and its i.r. and n.m.r. spectra. The NH absorption band at 3305 cm^{-1} and the lactam C=O band at 1725 cm^{-1} were both at a higher frequency than the corresponding bands of the hydrogen bonded N-hydroxy indoline (338). The n.m.r. spectrum $(CDCl_3)$ displayed an NH signal at $\delta 5.57$ (exchangeable with D_2O), a methyl signal at $\delta 2.09$, an aromatic multiplet (9 protons) and a methylene signal in the form of a doublet of doublets centered at $\delta 3.33$. The mass spectral fragmentation of this spiro-pyrazolone (339) and some other related compounds will be discussed in detail in a later section.

ii) Reduction of 1,3-diphenyl-4-(2-nitrobenzylidine)-2-pyrazolin-5-one (318b).

Reduction of compound (318b) with sodium borohydride/ palladium-charcoal in dioxane was carried out in a similar manner to that described for the methyl analog (318a). In this case, only two products were obtained. The major one was identified as spiro-[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (342) while the minor one was found to be the previously described amphoteric amine (321b). Identification of (342) was based on its
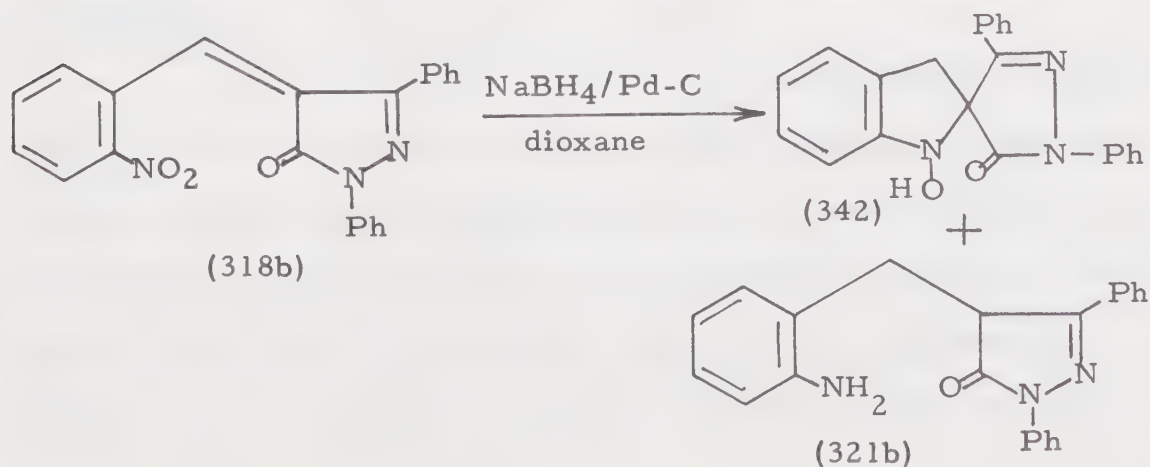
elemental analysis $(C_{22}H_{17}N_3O_2)$ as well as its physical and chemical properties. It reduced Tollen's reagent and gave a positive reaction with triphenyltetrazolium chloride. Its i.r. (N—OH band at 3347 and C=O band at 1696), n.m.r.(exchangeable N—OH signal at δ9.8, methylene signal at δ3.47 and a 14 proton aromatic multiplet between δ6.7 and 8.3) and mass spectra (expulsion of O, ȮH and H_2O from the molecular ion) were very similar to those of the methyl analog (338).

Reactions of Cyclic N-Hydroxyindoline Derivatives (338 and 342).

The chemical properties of aromatic hydroxylamines and hydroxamic acids have been studied in some detail. Fewer studies on cyclic hydroxylamines have been reported. Since some stable N-hydroxy compounds were prepared in the present study, a brief investigation of their chemical reactivity was made. The reactions studied, which could be of biochemical significance, were as follows:-

  a) Reduction

  b) Oxidation

  c) Attempted dehydration

  d) Reactions with nucleophiles

  e) Acylation and sulfonation reactions

  f) Methylation

a) Reduction:

The N-hydroxy function of cyclic hydroxylamines can be reduced to an NH function by various reducing agents including zinc and acids, phosphorous and hydroiodic acid, tin and hydrochloric acid, sodium hydrosulfite and lithium aluminum hydride. Catalytic hydrogenation over metals is also used for this purpose. However, in certain instances (Loudon and Wellings, 1960; Kato and Yamanaka,

1965) such reductions do not occur.

In the present study, the N-hydroxy compound (338) was found to be smoothly reduced by catalytic hydrogenation over platinum, to give an almost quantitative yield of the cyclic amine (339). The same compound was also isolated when the reduction was carried out using iron and ferrous ammonium sulfate or zinc and ammonium chloride. Both reductions were performed in aqueous ethanol. In none of these reductions was the double bond in the pyrazolone ring affected.

$$\text{(338)} \xrightarrow{\text{Reduction}} \text{(339)}$$
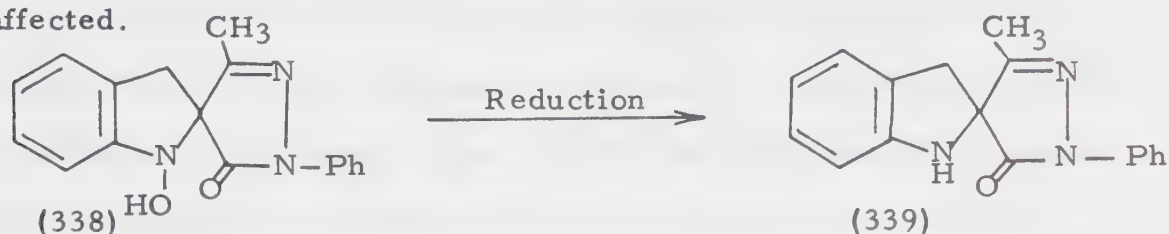
Similarly, reduction of the phenyl analog (342) using the same reducing agents yielded the amine, spiro[(indoline)-2,4'-(1',3'-diphenyl-1$\underline{H}$-pyrazoline-5'-one)] (343). This compound analyzed correctly for $C_{22}H_{17}N_3O$ (M$^+$ = 339). Its i.r. spectrum displayed an NH absorption band at 3485 cm^{-1} while its n.m.r. spectrum (DMSO-d$_6$) showed a D-exchangeable one-proton signal at δ4.6, a two-proton methylene singlet at δ3.5 and an aromatic multiplet which integrated for 14 protons .

(343)
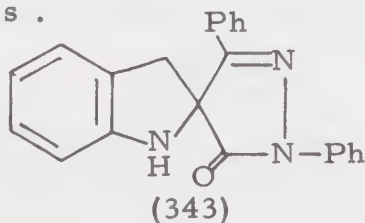
b) Oxidation:

Relatively mild oxidation will convert some cyclic N-hydroxy compounds to the corresponding nitrones. Frequently, this is done in the absence of any catalyst by simply bubbling air through solutions of

the N-hydroxy compounds or by allowing solutions to stand in the
atmosphere for several days at room temperature (Kato and Yamanaka,
1965). However, in most instances, a catalyst is required before
oxidation takes place. Cupric acetate-ammonia, potassium ferri-
cyanide and mercuric oxide have all been used successfully for this
purpose.

Due to the susceptibility of the pyrazolone ring to oxidiz-
ing agents (Wiley and Wiley, 1964), an attempt to oxidize the N-
hydroxyindoline (338) by bubbling air through its solution in tetra-
hydrofuran or aqueous ethanol was performed, but it failed to have
any effect. Therefore, copper sulfate-ammonia, which was used
extensively for this purpose by Brown et al (1959) was tried as a
catalyst. Air was bubbled for several hours through a solution of
(338) in aqueous ethanol, to which was added small amounts of copper
sulfate and ammonia. Crystallization of the crude product gave a
dark brown compound which, despite difficulty in getting a pure
sample for elemental analysis, is believed to be the cyclic N-oxide
(344). The mass spectrum of this compound displayed a molecular
ion at m/e 291 which corresponds to the formulation $C_{17}H_{13}N_3O_2$.
It liberated iodine from potassium iodide solution, a property common
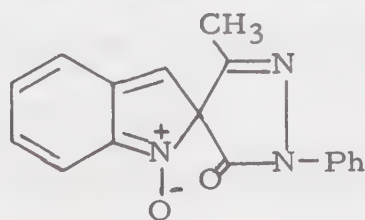
(344)

to N-oxides (Katritzky, 1956). Its i.r. spectrum was devoid of any
amine or hydroxy absorption, and it displayed a carbonyl band at
1728 cm^{-1} which was located at a higher frequency than that of the

N-hydroxy compound (338) due to the lack of any hydrogen bonding. The n.m.r. spectrum ($CDCl_3$) had no D-exchangeable protons; it displayed only two signals, a methyl singlet at δ 2.07 and an aromatic multiplet between δ 6.7 and 8.2 (10 protons).

c) Attempted Dehydration:

Due to the presence of a labile benzylic proton in the indoline ring, the dehydration of this N-hydroxy compound (338) was expected to proceed readily. Heating this compound with 10% sulfuric acid in methanol resulted in decomposition of the pyrazolone nucleus and the product isolated was not identified. When the same reaction was repeated at 0°, the pyrazolone ring was not affected. However, the desired product (345) was not formed; instead, a methoxylated compound, resulting from the nucleophilic attack of methanol on the
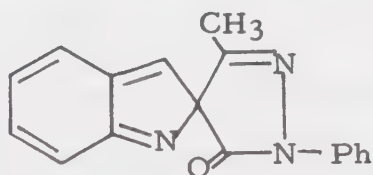
(345)

benzene ring, was obtained. The same type of reaction happened when methanol was replaced with a mixture of dioxane and water; this led to a hydroxylated derivative. The formation and identification of both these products will be discussed in the next section.

d) Reactions with nucleophiles:

Phenylhydroxylamine rearranges in acid media to yield o- and p-aminophenol with varying amounts of azobenzene, azoxy-benzene, aniline and nitrobenzene (Bamberger, 1921, 1925; Yukawa, 1950). When this reaction was carried out in the presence of nucleo-philic species other than water, such as methanol, aniline or chloride

ions, the corresponding <u>ortho</u> and <u>para</u> substituted anisidine, semi-dines and chloroanilines respectively were formed. Similar reactions were also observed by Kock (1887) and Robertson and Evans (1940). Heller <u>et al</u> (1951) formulated the mechanism of these nucleophilic reactions in an S_N1' manner, but they did not rule out the possibility of an S_N2' type reaction. Their proposed mechanism, for a <u>para</u> rearrangement, is illustrated in Scheme 6 in which Y could be any
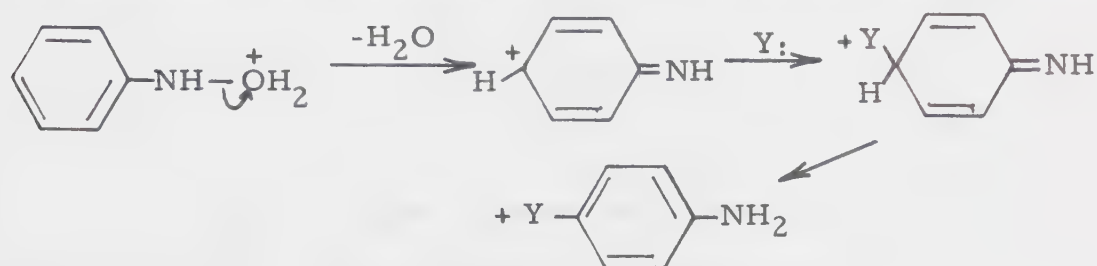
Scheme 6

accessible and reactive nucleophilic molecule or anion.

Various examples are now known of different nucleophilic reagents reacting with aromatic hydroxylamine and hydroxamic acid derivatives. Reactions in which the nucleophile is a halogen (Coutts and Pound, 1970; Stöhrer and Brown, 1970), oxygen (Gassman and Campbell, 1971), sulfur (Boyland <u>et al</u>, 1962; Edward and Whiting, 1971), nitrogen (Wölcke <u>et al</u>, 1969) or carbon (Takahaski and Kano, 1964) species have been reported. However, few of these reactions have been attempted with cyclic hydroxylamines.

In this study, different nucleophilic species, i.e. chloride ion, water, methanol and acetic acid, were reacted, in acidic media, with the N-hydroxy compound (338). In each case, it was deduced that a 5-substituted indoline derivative (346) was obtained. The preparation and structural elucidation of these compounds are now described.
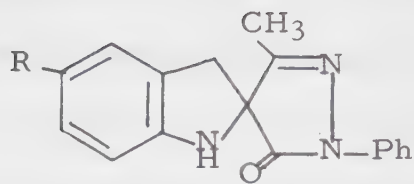
(346)

a; R = Cl

b; R = OCH$_3$

c; R = OH

d; R = OCOCH$_3$

- - -

When hydrogen chloride was bubbled through a cold solution of the N-hydroxy compound (338) in tetrahydrofuran, a black semi-solid product was obtained. Chromatography of this product on a silica gel column, yielded spiro-[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346a) as a crystalline solid. This compound was identified by its elemental analysis (C$_{17}$H$_{14}$ClN$_3$O) as well as its spectral properties. The i.r. spectrum displayed C=O and NH absorptions. A methyl signal, a methylene doublet of doublets, an 8-proton aromatic multiplet and an N—H signal were present in the n.m.r. spectrum. The location of the chlorine atom in the product (346a) was suggested from the ample literature evidence that when hydrochloric acid and other nucleophilic reagents react with aromatic hydroxylamines, p-substituted amines are the major products isolated (Bamberger, 1925; Robertson and Evans, 1940; Coutts and Pound, 1970). However, confirmatory evidence could not be obtained from examining the n.m.r. spectrum of the product since the aromatic signal was complex and could not be easily interpreted.

This location of the chlorine atom became more significant when another isomeric chlorinated compound was obtained, as a by-product, by the action of acetyl chloride on the hydroxylamine (338) in benzene. Both these compounds analyzed correctly for $C_{17}H_{14}ClN_3O$ and displayed very similar mass spectra but their melting point, i.r. and n.m.r. spectra were different. Therefore, it was found necessary to prepare an authentic sample of (346a) for comparison purposes.

3-Chloro-6-nitrobenzaldehyde (316b) was condensed with 3-methyl-1-phenyl-2-pyrazolin-5-one (317a) and the product (318c) was reduced with sodium borohydride and palladium-charcoal in dioxane. Spiro [(5-chloro-1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (347), $C_{17}H_{14}ClN_3O_2$, was isolated and identified from its physical and chemical properties which were similar to those of the other N-hydroxyindolines (338) and (342). Catalytic hydrogenation of (347) over platinum yielded the 5-chloro-indoline (346a). Comparison of the spectral data and melting points of this compound with those of the product obtained by treating (338) with hydrogen chloride proved that both were identical.

(318c)

$\xrightarrow[\text{Dioxane}]{\text{NaBH}_4/\text{Pd-C}}$

(347)

H_2/Pt

(346a)

- - -
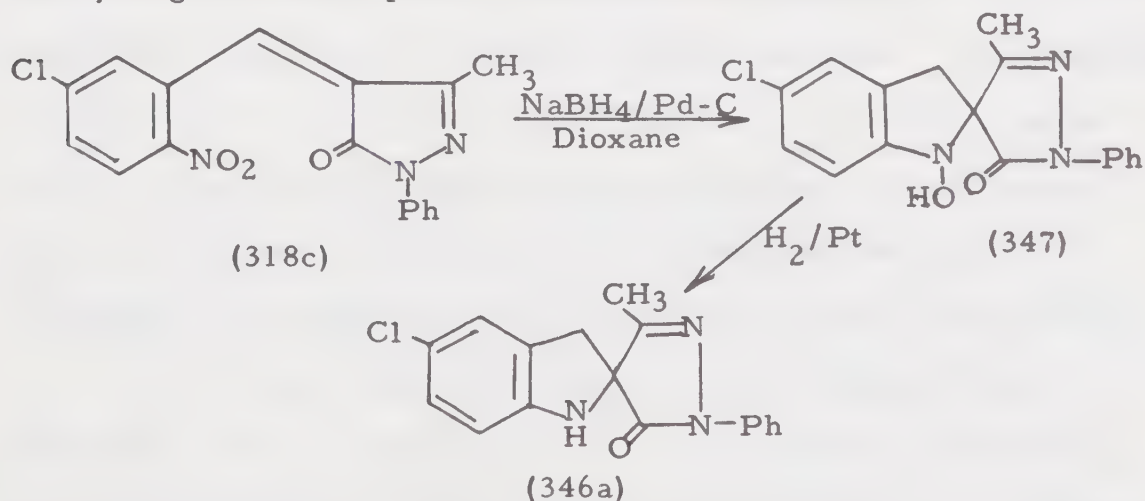
Heating the N-hydroxy compound (338) with methanol in the presence of a catalytic amount of sulfuric acid, resulted in decomposition. When this reaction was repeated and the reaction mixture left for 12 hours at $0^{\circ}C$, a dark green solution was obtained from which was isolated a colorless compound identified as spiro [(5-methoxy-indoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (346b). This structure was assigned for the following reasons: the product
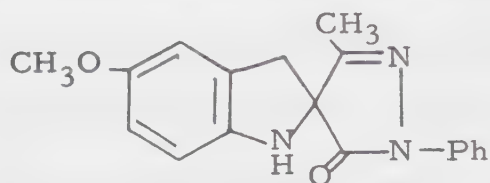
(346b)

analyzed correctly for $C_{18}H_{17}N_3O_2$ and its mass spectrum displayed a molecular ion at m/e 307, and showed, with minor differences, fragmentation patterns similar to those of the indoline (339) and the 5-chloroindoline (346a). These are described in more detail in a subsequent section. The i.r. spectrum had C=O and NH absorption bands at 1710 and 3310 cm^{-1} respectively. The n.m.r. (CDCl$_3$) displayed two methyl signals, a methylene doublet of doublets signal, a broad NH signal and an aromatic 8-proton multiplet. The complexity of the aromatic signal did not allow deduction of the exact location of the OCH$_3$ group but the pattern displayed for this signal was very similar to that in the spectrum of the 5-chloroindoline (346a). Accordingly, the methoxy substituent was assigned to the 5-position.

A better yield of this compound was obtained when methanolic sulfuric acid was replaced with a solution of boron tri-fluoride in methanol. This observation was the result of an attempt to methylate the N-hydroxy function by the use of diazomethane in

methanol, with boron trifluoride as a catalyst. Acid catalyzed

nucleophilic attack by methanol occurred rather than methylation

of the N-hydroxy function, and the only product isolated was the 5-

methoxy compound (346b).

- - -

When the N-hydroxy compound (338) was reacted with

a mixture of dioxane and water in the presence of catalytic amounts

of sulfuric acid, an alkali-soluble product was isolated. Although

no satisfactory analysis was obtained from this product, its i.r.,

n.m.r. and mass spectra (M^+ at m/e 293) suggested that it was the

5-hydroxyindoline (346c).
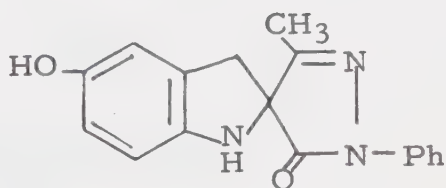
(346c)

- - -

The related 5-acetoxy derivative (346d) was obtained by

heating (338) with glacial acetic acid for one hour. This compound

was identified by its elemental analysis ($C_{19}H_{17}N_3O_3$), mass spectrum

(M^+ at m/e 335), i.r. spectrum (ester and lactam C=O and N—H

absorption) and n.m.r. spectrum (two methyl signals, one D-ex-

changeable N—H proton, a methylene signal and an 8-proton aromatic

multiplet.
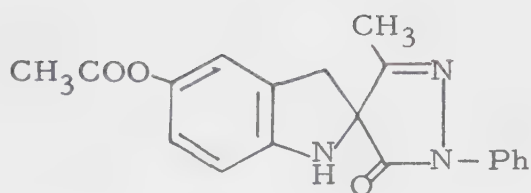
(346d)

- - -

The formation of these 5-substituted indoline derivatives
(346a-d) apparently involves a nucleophilic attack at the 5-carbon
atom of the protonated N-hydroxy compound (348). However, it is
not known whether this reaction is of the $S_N 2'$ (Scheme 7) or $S_N 1'$
(Scheme 8) type. An $S_N 2'$ mechanism was proposed recently by

(348)

(346)
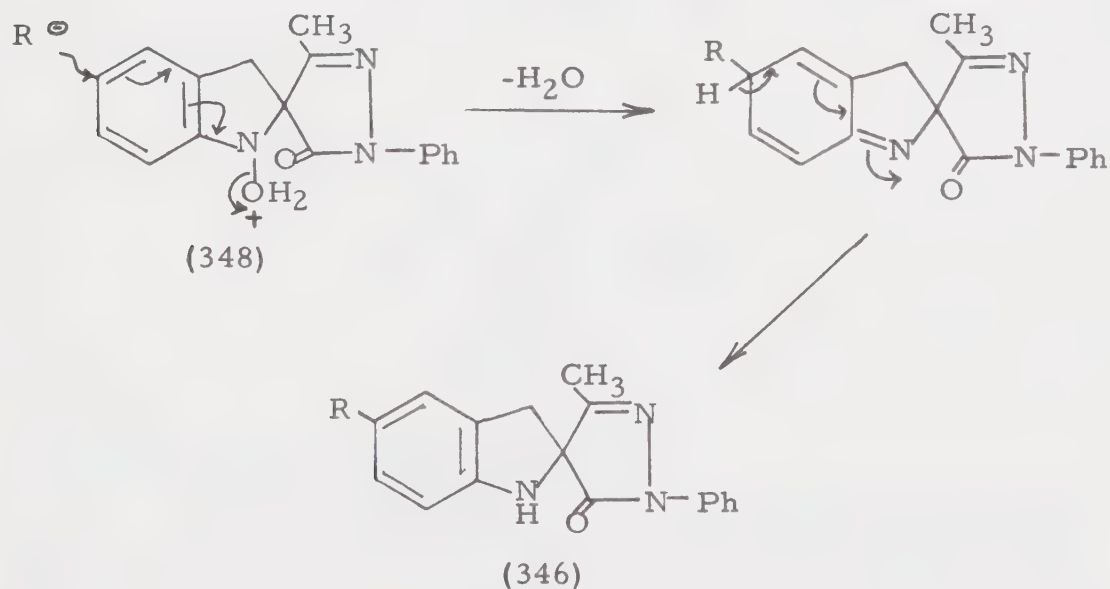
Scheme 7

Coutts and Pound (1970) for the attack of the chloride ion on some
related hydroxylamines and hydroxamic acids. The alternative
$S_N 1'$ type mechanism was proposed earlier by Heller et al (1951)
and is supported by some recent studies by Gassman et al (1968,

1971, 1972).

(346a-d)
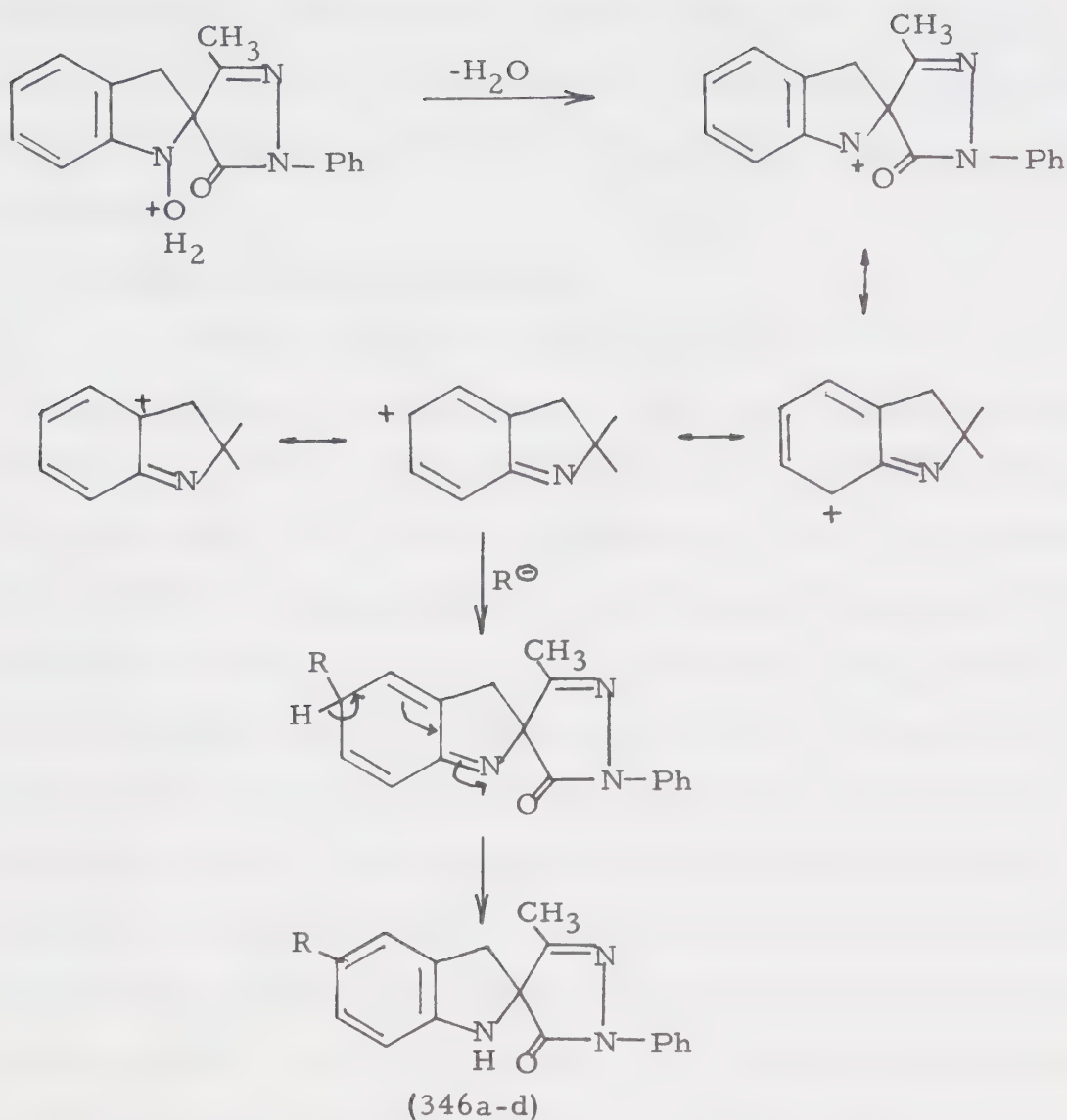
Scheme 8

e) **Acylation and sulfonation reactions:**

Cyclic hydroxylamines react with acetyl, benzoyl and sulfonyl chlorides to form acetates, benzoates and sulfonates res- pectively. Acid anhydrides have also been used frequently as acyla- ting agents. However, in many cases the acyloxy and sulfonyloxy derivatives cannot be isolated because they undergo molecular rearrangements. In order to determine the behavior of the cyclic N-hydroxy compounds prepared in this investigation towards some

acylating and sulfonating agents, their reactions with acetic anhydride, acetyl chloride, p-chlorobenzoyl chloride and p-toluene sulfonyl chloride were studied. Besides the few N-acetoxy derivatives obtained, some rearrangement and halogenated products were also isolated and identified.

i. Reactions with acetic anhydride

Previous studies have shown that the cyclic N-acetoxy carbonyl function gives rise to an i.r. absorption band in the region of 1800 cm^{-1} and the presence of this absorption band is very diagnostic (Freeman, 1958; Loudon and Wellings, 1960). It was desirable, therefore, to acetylate the cyclic N-hydroxy compounds (338 and 342) as a means of confirming their structures and to study the chemical behavior of these N-acetyloxy products. A number of conventional acetylation procedures were attempted but most of them led to the formation of different rearrangement and decomposition products. The only successful method was to react the N-hydroxy compound in pyridine at -10°C with cold excess acetic anhydride for a 24 hour period. In a few instances, the N-acetyloxy derivatives crystallized from the reaction mixture, but in most cases ice-cold water had to be added to liberate the product. The acetyloxy products isolated were stable for several weeks at 0°C but decomposed rapidly on standing at room temperature. Earlier, when this acetylation process was performed at room temperature, no acetyloxy derivatives were obtained. The same happened when the reaction mixture, after being added to ice-cold water, was extracted with cold ether. Both procedures resulted in rearrangement and decomposition of the N-acetyloxy derivatives.

The acetylated product obtained from the N-hydroxy compound (338) was identified as spiro [(1-acetyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5-one)] (349). This compound analyzed correctly for $C_{19}H_{17}N_3O_3$, a formula supported by the presence of a molecular ion at m/e 335 in its mass spectrum. That
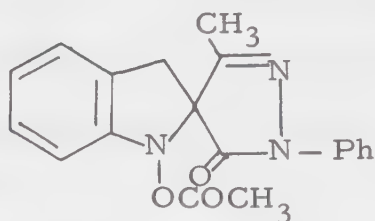
(349)

O-acetylation had occurred was confirmed by the presence of an N-acetyloxy C=O absorption band at 1790 cm^{-1}. In addition, a lactam C=O band was located at 1723 cm^{-1} and the spectrum was devoid of any O—H or N—H bands. The n.m.r. spectrum (in CDCl$_3$ or DMSO-d$_6$) showed two methyl signals at δ 2.14 (C—CH$_3$) and 2.05 (OCOCH$_3$), an aromatic multiplet (9 protons) and the methylene group signal as a doublet of doublets (J=16.5 Hz). This spectrum had to be measured directly after dissolving in cold solvent because, in both solvents used, the compound decomposed and/or rearranged very rapidly; the N-acetyloxy signal disappeared with the appearance of some new signals and the spectrum became very complicated.

Heating the N-acetyloxy compound (349) with methanol or ethanol yielded two different crystalline products. The first was identical to the 5-acetyloxy derivative (346a) obtained earlier by the nucleophilic attack of acetic acid at C-5 (see Scheme 7). The second product (designated compound A) remains unidentified, although it is known from its elemental analysis ($C_{17}H_{13}N_3O$) and its mass spectrum

(M^+, m/e 275) that it is a result of the loss of acetic acid molecule from the parent N-acetoxy compound (349). The same compound was also isolated during attempts to methylate or sulfonate the N-hydroxy compound (338).

The possibility of product (A) being the dehydrated (345) was first considered but a study of the chemical and physical properties of (A) ruled out this possibility. The i.r. spectrum of A when crystallized from ethanol showed absorption bands at 3410 (NH?) and at 1625 and 1640 cm^{-1} (C=O?). A different spectrum was obtained when the same compound was crystallized from acetic acid giving (A') or when (A) was heated to about 200°C for a few minutes. The absorption bands at 3410 cm^{-1} and the doublet at 1625 and 1640 cm^{-1} were replaced with a broad band between 2500 and 3300 cm^{-1} and a strong absorption at 1640 cm^{-1}. This suggested that compound (A) may either have dimerized or be present in two different forms (A $\rightleftharpoons$ A'). Both these forms were found to be interchangeable; either one can be obtained by crystallization from the appropriate solvent.

The n.m.r. of both forms had a three-proton signal at $\delta 2.63$, an aromatic multiplet between $\delta 7.0$ and 8.5 ($\sim$9 protons) and a one-proton broad signal between $\delta 4.0$ and 5.1 (exchangeable with D_2O). The presence of the methyl signal at a lower field ($\delta 2.63$) than usually demonstrated by the pyrazolone methyl group (around $\delta 2.0$) suggested that a rearrangement process might have occurred which destroyed the pyrazolone ring. Compound (350), the formation of which might be possible by the process outlined in Scheme 9 was considered and found to fit most of the chemical and physical proper-ties demonstrated by the product (A $\rightleftharpoons$ A'). This compound (350)

(349)

−CH₃COOH

(345)

Scheme 9

(350)
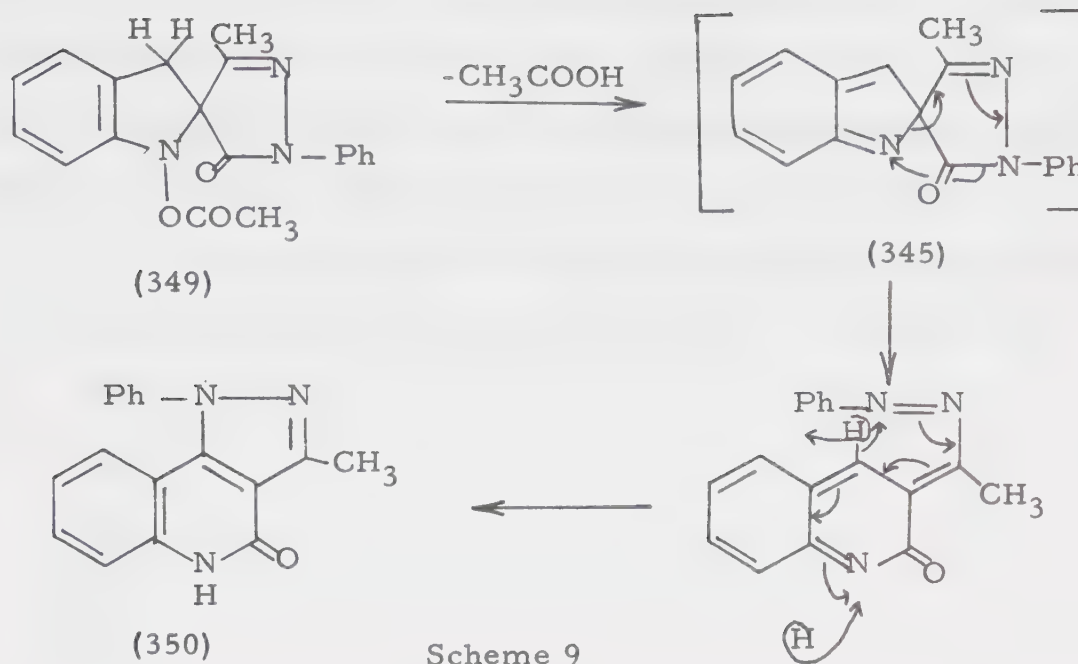
might exist in two forms (350a ⇌ 350b) which could explain to some

extent the difference in the i.r. spectra of (A) and (A'). The

(350a)   (350b)
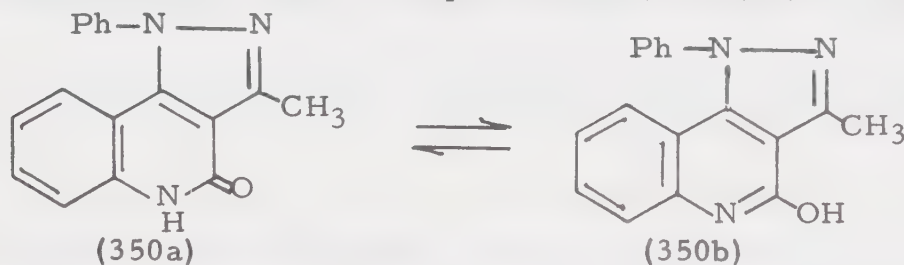
possibility of dimerization of (A) must also be considered in view of

the fact that the structurally related pyridin-2-ones e.g. (351) are

known to exist as hydrogen-bonded dimers (352). The i.r. spectra

(351)

(352)
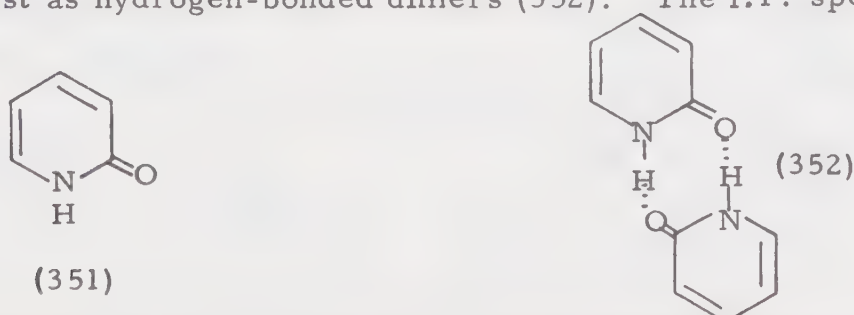
of these dimers displayed very broad N—H absorption bands in the

region 2300-3200 cm^{-1}; free N—H bands were demonstrated in dilute

chloroform solutions at around 3400 cm^{-1} (Katritzky and Amber, 1963).

The presence of carbonyl absorption at 1640 and 1625 cm^{-1} (doublet?)
in (A) and at 1640 cm^{-1} in (A'') is also in agreement with structure
(350) since quinolin-2-ones show carbonyl absorption between 1626 and
1660 cm^{-1} (Bellamy, 1968; Katritzky and Ambler, 1963).

A structure such as (350) could also explain the behavior
of product (A) under electron impact (Fig. 4).   In addition to the
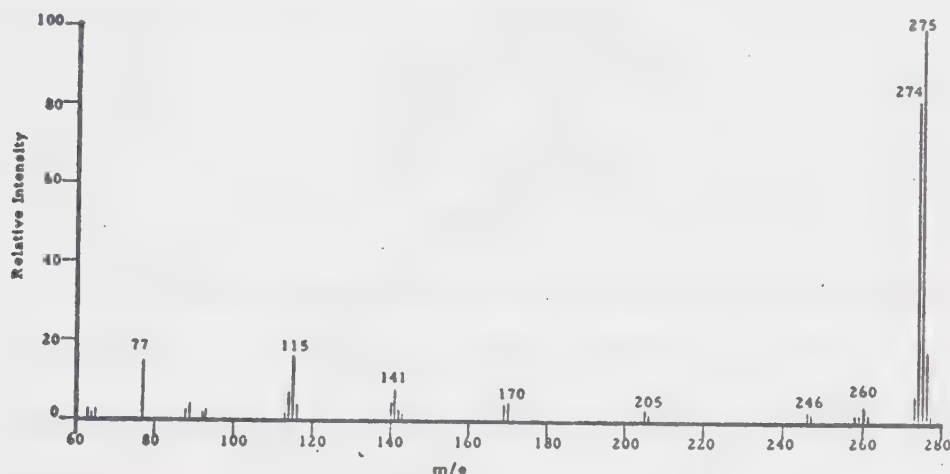
Fig. 4:   A portion of the mass spectrum of compound (A), M$^+$=275.

molecular ion, the main fragment observed was the (M-1) ion at m/e
274.   A stable aromatic system (b) could be formed by the expulsion
of a hydrogen atom from the molecular ion (Scheme 10).
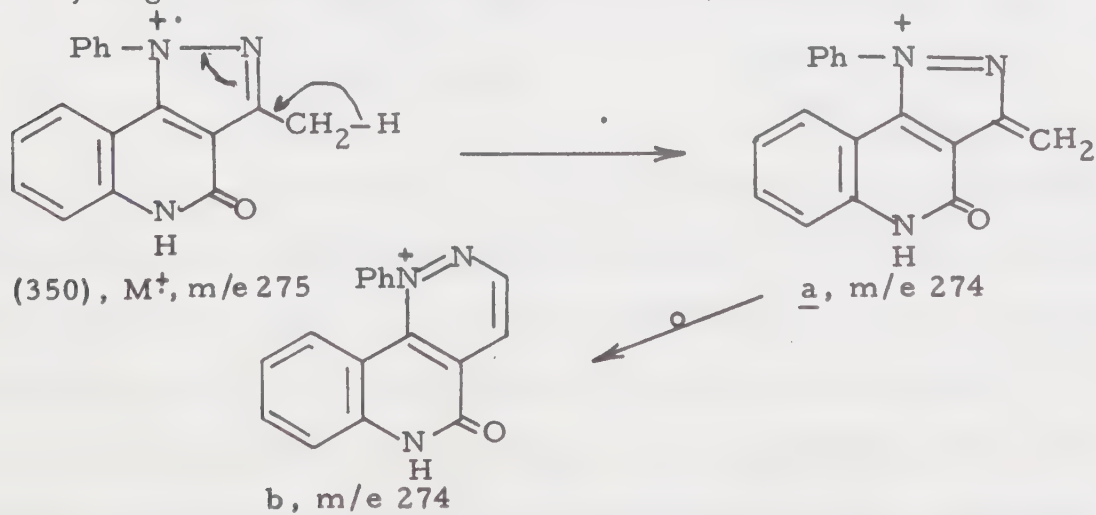
Scheme 10

In addition to these physical and chemical properties
already discussed, the high melting point (306-7°) of both (A) and (A')
is consistent with the proposed structure (350).   A related compound,
4,5-dihydro-3-methyl-4-oxo-1H-pyrazolo[4,3-C]quinoline (353) was
prepared by Coutts and Wibberley (1963) and was found to have a
melting point higher than 350°C.

(353)
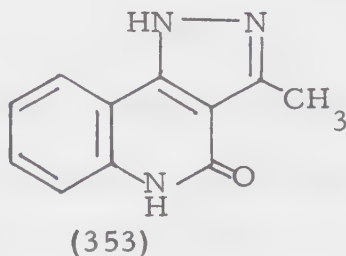
A chemical property that cast doubt on the assignment of
(350) to product (A) was the ease with which this compound acetylated
with acetic anhydride.   This was not expected since 2(1H)-pyridones
and related compounds acetylate only through their salts, such as the
sodium (Curtin and Engelmann, 1968) or thalium (I) salts (McKillop
and Zelsko, 1968).   In addition, acetylation of (350), if it occurred,
might be expected to yield the O-acetyl derivative (354) rather than

(354)

(355) COCH₃
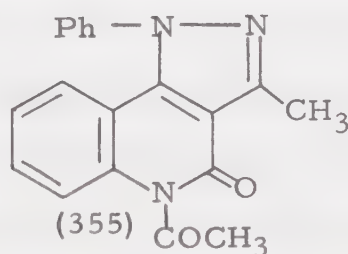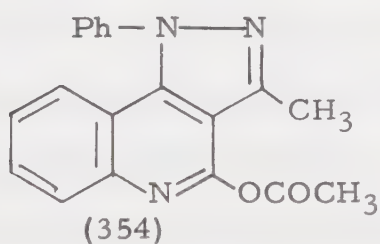
the N-acetyl compound (355).   This was the case with 2(1H)pyridone
(351) which yielded only the O-acetyl derivative (357) when its thallium
(I) salt was acetylated.   The N-acetyl derivative (356) was formed at
-40°C but most of it rearranged at room temperature to (357)
(McKillop and Zelesko, 1968).   However, the possibility of O-acetyl-
ation of (350) was ruled out by the presence of two C═O absorption

bands at 1664 and 1730 cm^{-1} in the i.r. spectrum of the mono-

acetylated product, $C_{18}H_{15}N_3O_2$ (M$^+$ = m/e 317).

(356)   (357)
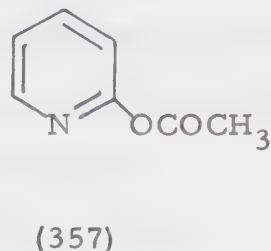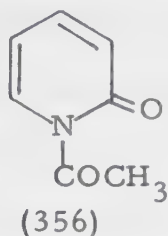
Reference by Curtain and Engelmann (1968) to the N-

benzoyl derivative (358) was encouraging since it showed that this

type of acyl derivative is accessible.   Gortinskaya et al (1973)

also prepared some related N-acetyl derivatives (359), the structures

of which were confirmed with i.r. and u.v. spectral data.   The two

carbonyl bands in (358) were located at 1656 and at 1733 cm^{-1};   the

(358)   (359)
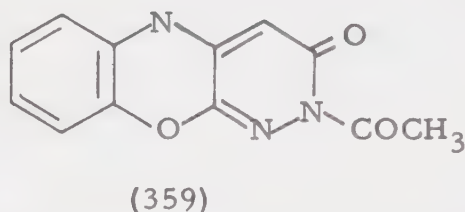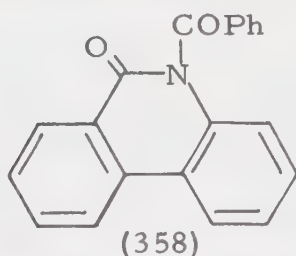
latter is due to the N-benzoyl function.   These values are comparable

to those obtained from the acetyl derivative of (350), but this is not a

very accurate comparison since a benzoyl compound is being compared

with an acetyl derivative.   However, the N-acetylated compound (359)

had C=O absorption bands at 1680 and at 1730 cm^{-1};   the latter was

shown to be due to the N-acetyl function.   Both these values are

similar to those shown by the acetyl derivative of (350), which suggest-

ed that its structure might indeed be (355).

A literature search for the pyrazolocarbostyryl derivative

(350) revealed that it was a known compound prepared earlier by three

independent investigators through different pathways (Knorr and Jodicke,

1885; Musierowicz et al, 1929; Vul'fson and Zhurin, 1962). In all

cases, the reported melting points, although high (261°, 273° and

277°), were not the same as that of the dehydrated product (A) although

in this range, the rate of heating might account for this difference.

It is also possible that impure (350) was isolated in earlier studies.

Accordingly, it was decided to prepare (350) to compare it directly

with the dehydrated product (A). The method reported by Vul'fson

and Zhurin (1962) was followed (Scheme 11) and yielded the required

Scheme 11
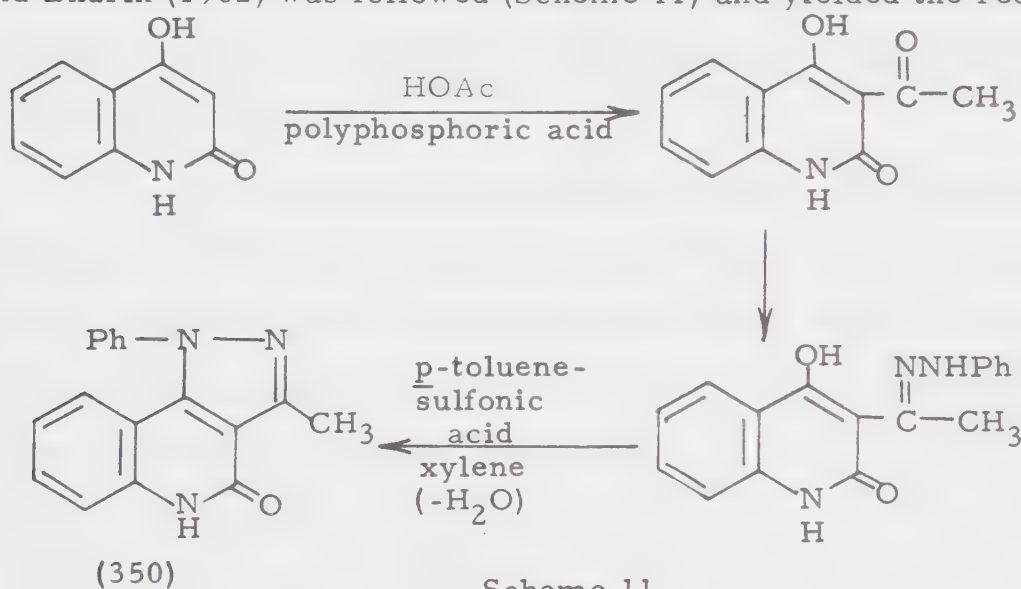
3-methyl-5-phenyl-pyrazolo-(4,5-C)carbostyril (350).

A direct comparison between synthetic (350) and the

deacetylated product (A) indicated non-identity. The i.r. spectrum

of (350) (ν N—H between 2000 and 3220, ν C=O at 1666) and its

n.m.r. spectrum (CH$_3$ at δ 2.61, NH or OH at δ 13.2 and nine

aromatic protons between δ 6.9 and 7.8) were very similar to those

of (A) but not identical. The pyrazolocarbostyril (350) was also

found to be neutral, but an attempt to acetylate it directly by heating

with acetic anhydride for 12 hours failed to yield any acetylated

product.

This non-identity of (350) with (A) demanded a reappraisal of the data accumulated for compound (A). It had a molecular formula $C_{17}H_{13}N_3O$, nine aromatic protons, three methyl protons, a labile proton (deuterium exchangeable) and a C=O group which absorbed i.r. irradiation at a frequency lower than the pyrazoline C=O group. In the n.m.r. spectrum the chemical shift of the methyl-protons signal was further dowfield than normally observed for the 3-methyl-5-pyrazolone methyl signal which suggested that compound (A) did not contain an intact pyrazoline ring such as that present in the spiropyrazolone (349).

It is now realized that the acetylated product (349) might rearrange in the manner shown in Scheme 12, thus providing another possible compound, the pyridazinoindole (360) to explain all the data accumulated for compound (A ⇌ A'). Lack of time, however, prevented studies to confirm this hypothesis.
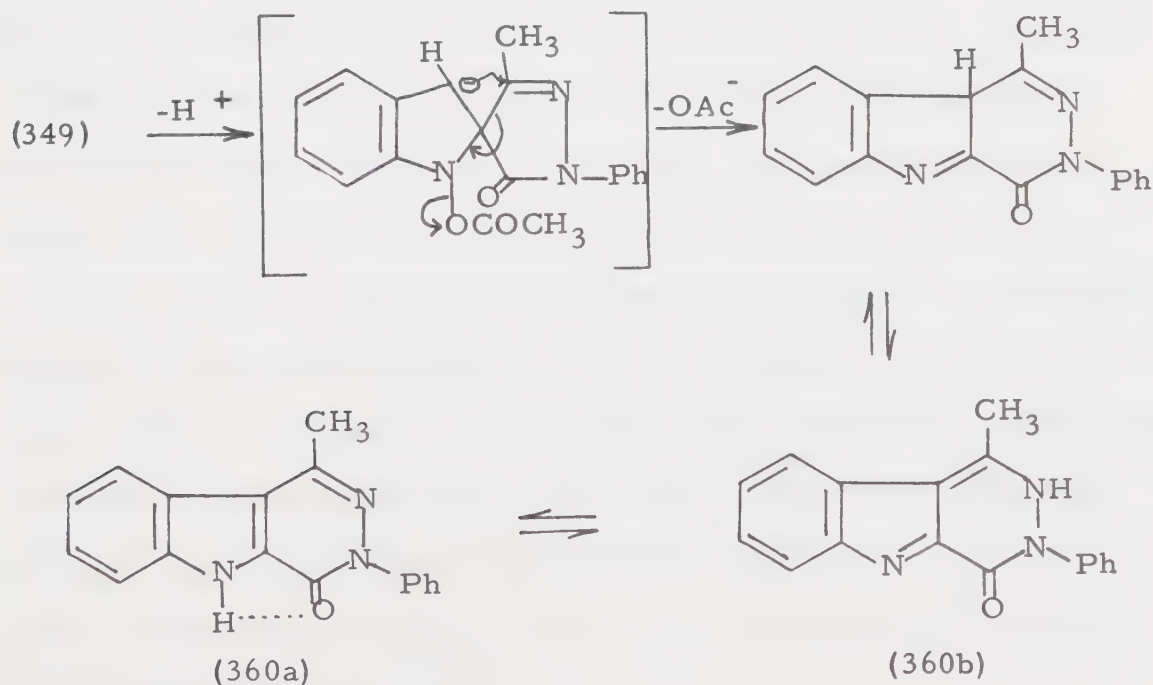
Scheme 12

Acetylation of the cyclic N-hydroxyindoline (342) with acetic anhydride and pyridine at -10°C yielded an N-acetoxy derivative identified as spiro[(1-acetyloxyindoline)-2,4'-(1,3'-diphenyl-1$\underline{H}$-pyrazolin-5-one)] (361) by its elemental analysis ($C_{24}H_{19}N_3O_3$) and by similarities of its spectral data with those of the methyl analog

(361)
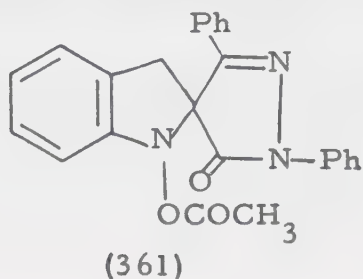
(349). It was noted that the acetyloxy derivative (361) was relatively stable at room temperature and in cold solvents. Rearrangement still occurred in solution but at a much lower rate than that demonstrated by the methyl analog (349). Heating (361) in ethanol produced only one rearrangement product of formula $C_{24}H_{19}N_3O_3$. Infrared evidence supported the presence of an NH and two C=O groups (lactam and ester) in the molecule. The n.m.r. spectrum had signals which could be ascribed to $COCH_3$, CH_2, NH and thirteen aromatic protons. Based on these data this compound was identified as spiro[(x-acetyloxyindoline)-2,4'-(1',3'-diphenyl-1$\underline{H}$-pyrazolin-5'-one)] (362). Although it is most likely that (362) is substituted at the 5-position as was the case with the methyl analog (346d), the exact position of the substituent was not determined due to the complex nature of the aromatic signal in the n.m.r. spectrum and due to the lack of an authentic sample.

When the N-hydroxy compounds (338 and 342) were heated with acetic anhydride or with a mixture of acetic anhydride and acetic acid, no N-acetyloxy derivatives were isolated. In the case of (338), two products were obtained, the major product being the dehydrated compound (A) discussed earlier while the minor product was shown to be a diacetylated compound, $C_{21}H_{19}N_3O_4$ which was assigned structure (363). The i.r. spectrum showed three $C=O$ bands at 1667 (cyclic

(363)
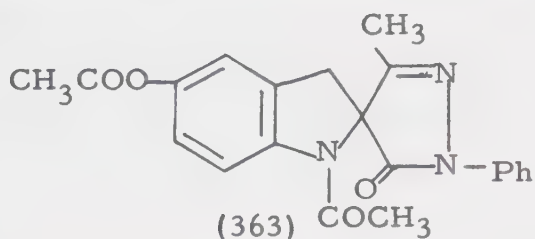
amide), 1715 (lactam) and 1760 cm^{-1} (ester) and was devoid of any NH or OH absorption. The n.m.r. spectrum displayed three methyl signals at $\delta 2.02$, 2.3 and 2.50 and a complex aromatic multiplet which did not assist in the assignment of the position of the acetate group on the ring. This, however, was deduced to be at C-5 in agreement with the mode of formation, and by comparison with similar products described earlier such as (346d).

Heating the N-hydroxy compound (342) with acetic anhydride yielded a diacetate derivative which could not be obtained pure. Its mass spectrum displayed a molecular ion at m/e 439 which fragmented in the same way as the diacetate (363) and its i.r. and n.m.r. spectra resembled those of compound (363). This led to its identification as (364). The position of the acetate group on the ring was not determined.

(364)
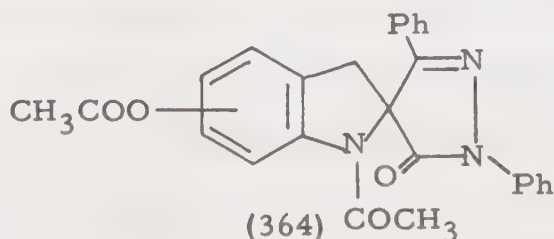
The diacetates (363) and (364) could be formed in two ways as shown in Scheme 13. The first is the formation of the N-acetyloxy

(365)

(366)

(367)

Scheme 13
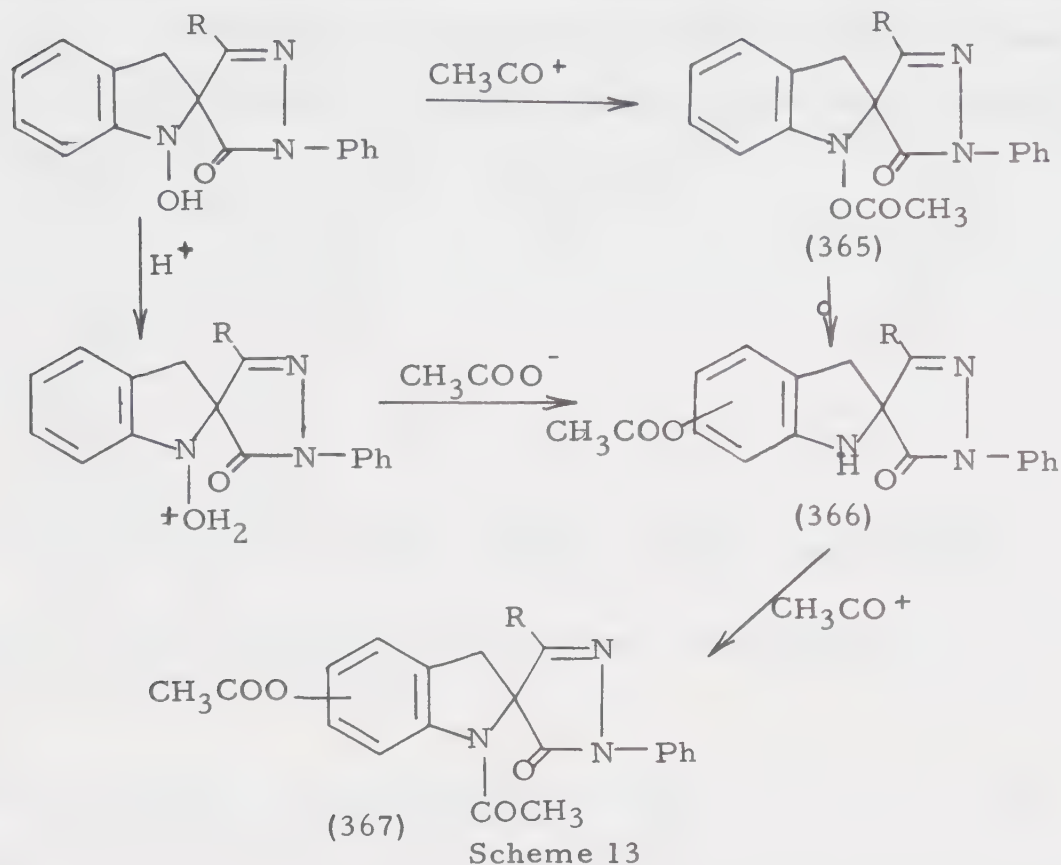
derivative (365) followed by migration of this acetyloxy group to the ring carbon. The second is the direct nucleophilic attack by the acetate anion. The resulting monoacetylated indoline (366) would then acetylate further giving compound (367).

ii. Reaction with acetyl chloride:

When spiro [(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one] (338) was treated with acetyl chloride at room temperature it failed to react. When this mixture was heated in dry benzene for several hours, a reddish solution was formed which on evaporation and crystallization yielded two compounds. Neither of these was found to be the N-acetyloxy derivative (349). A study of the properties and spectra of each compound indicated that one of them

(the minor product) was an acetylated compound while the other (the major product) was a chlorinated derivative.

The mass spectrum (Fig. 5) of the acetylated product, $C_{19}H_{15}N_3O_3$, displayed a molecular ion (m/e 333) which expelled a
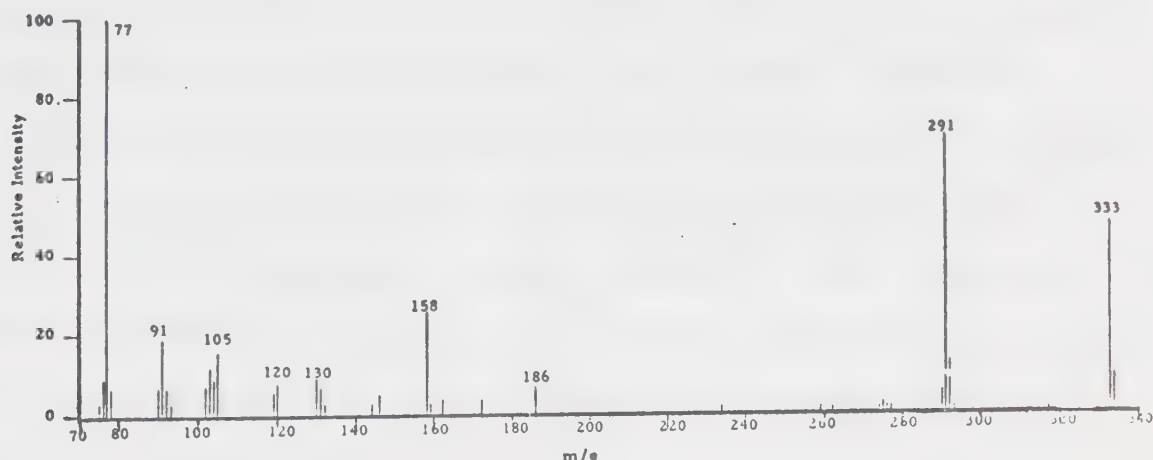
Fig. 5: A portion of the mass spectrum of an unidentified acetylation product, $M^+ = 333$.

ketene molecule as expected from an acetate. Its i.r. spectrum showed two carbonyl bands at 1688 and 1712 cm^{-1} and was devoid of OH and NH absorption (?). The dark-red color of this product was indicative of conjugation; this was also shown by the absence of the methylene signal in its n.m.r. spectrum which showed two methyl signals at $\delta 2.44$ and 2.48, an eight-proton aromatic multiplet between $\delta 7.0$ and 8.2 and a one-proton doublet centered at $\delta 9.8$ (J=8 Hz).

This acetylated compound hydrolyzed readily in the presence of alkali giving a yellowish product which analyzed for $C_{17}H_{13}N_3O_2$ ($M^+ = 291$). The presence of a phenolic function in this deacetylated product was suggested by its solubility in dilute alkali solution and by the broad absorption between 2000 and 3300 cm^{-1} in its i.r. spectrum. The n.m.r. spectrum (DMSO-d_6) displayed a very broad signal around $\delta 4.6$ and in addition, a methyl signal at $\delta 2.58$, an

aromatic multiplet (8 protons) and a one proton doublet centered at $\delta 8.5$.

It is obvious that the product, $C_{19}H_{15}N_3O_3$, is an acetylated phenol. However, no structure can be suggested which satisfies all the data which accumulated for this compound. In particular, the one-proton doublet in the n.m.r. spectra of both the acetylated and hydrolyzed products seems strange and hard to rationalize. That an N-acetyloxy derivative might be formed first then rearranged is a possibility, but when a sample of the N-acetyloxy-indoline (349) prepared earlier was refluxed in benzene it gave none of the above product. Instead, the dehydrated compound (A) and the 5-acetyloxyindoline (346d) were isolated.

The elemental analysis ($C_{17}H_{14}ClN_3O$) as well as the mass spectrum (M^+, m/e 311) of the major product confirmed the presence of a chlorine atom in its molecular formula. The possibility of this compound being the same 5-chloroindoline (346a) obtained earlier was ruled out by comparing i.r. and n.m.r. spectra and by the depression of a mixed melting point. However, the similarities of the spectral data of the product and that of (346a) suggested that both were isomeric. The n.m.r. spectrum was essentially similar to that of the 5-chloroindoline derivative (346a) except in the aromatic area where the substitution pattern differed. Again, this pattern was complex and could not be resolved. However, since one of these two isomers (346a) was proved to be substituted at the 5-position, it was considered likely that the isomer was a 7-chloro derivative (370).

These two position are more susceptible than any other position to attack by nucleophilic reagents. Accordingly, this product was tentatively identified as spiro [(7-chloroindoline)-2,4'-(3'-methyl-1'- 1H-pyrazolin-5-one)] (370). Support for this conclusion was found in the i.r. spectrum of this compound which had an NH absorption band
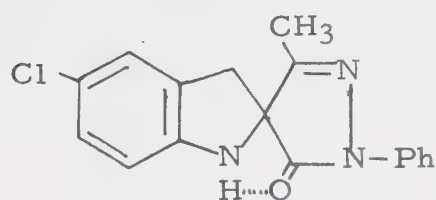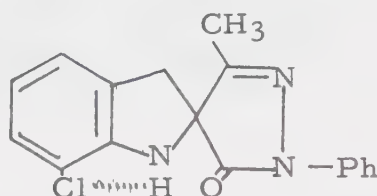
(346a)   (370)

at 3295 cm^{-1} and a C=O band at 1728 cm^{-1}. Compared to the corres- ponding absorption bands (3365 and 1710 cm^{-1}) in the related chloro- indoline (346a), the N—H absorption showed a bathochromic shift of 70 cm^{-1} and the C=O a hypsochromic shift of 18 cm^{-1}. Intramole- cular hydrogen bonding between the chlorine atom at C-7 and the amine hydrogen may be responsible for these shifts. In addition to the effect on the NH absorption, this also could affect the C=O absorption which is now located near the normal value ($\sim$1725 cm^{-1}) for com- pounds which do not display intramolecular hydrogen bonding. Hydro- gen bonding between chlorine and hydrogen is now becoming universally accepted (Vinogradov and Linnell, 1971) and the large frequency shift demonstrated here for the NH absorption may indicate that chlorine is a stronger electron donor than oxygen in this molecule.

The formation of a chlorinated product as a result of treating the N-hydroxy compound (338) with acetyl chloride was not unexpected due to the availability, in the reaction mixture, of chloride ions for nucleophilic attack. Similar examples are reported with

hydroxamic acids and heterocyclic N-oxides (Katritzky and Logowski,

1971d).   The reaction, for example, between 3-hydroxyxanthine (371)

and various acid chlorides, yielded only 8-chloroxanthine (372);   no

acyl products were obtained (Wölcke et al, 1969).

(371)   (372)

At the moment, an explanation as to why a C-7 (370),

and not a C-5 (346a) chlorinated product, was obtained in the reaction

with acetyl chloride, is not possible although it may be in part due to

the different solvents used (tetrahydrofuran for C-5 substitution and

benzene for C-7 attack).

iii.   Reaction with p-chlorobenzoyl chloride.

The reaction between the N-hydroxy compound (338) and

p-chlorobenzoyl chloride was carried out under very mild conditions in

an attempt to isolate the N-p-chlorobenzoyloxy derivative, but this

proved unsuccessful.   Although the i.r. spectrum of the crude

product showed C=O absorption band at 1765 cm^{-1} which is indicative

of N-benzoyloxy function (Kato et al, 1967; Zinner, 1958), crystalliza-

tion of this product from cold ethanol resulted in skeletal rearrange-

ment.   The pure crystalline compound isolated analyzed for

$C_{24}H_{18}Cl N_3O_3$, as was expected for the N-benzoyloxy derivative,

but its i.r. spectrum displayed an NH absorption band at 3380 cm^{-1}

and two C=O bands at 1712 (lactam) and at 1732 cm^{-1} (benzoyl ester).

The n.m.r. spectrum (CDCl$_3$) showed a methyl signal at δ2.15, a

methylene doublet of doublets centered at δ3.45 (J=17 Hz), an aromatic

multiplet (12 protons) and a D-exchangeable one-proton signal at δ 4.47

(NH). These data indicated that the benzoyloxy function rearranged

to one of the ring carbons but the position of substitution on the benzene

ring was not determined due to the complex nature of the aromatic

signal in the n.m.r. spectrum. This compound is partly identified as

spiro-[(x-p-chlorobenzoyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-

pyrazolin-5'-one)] (373). Its mass spectrum supported this conclusion;
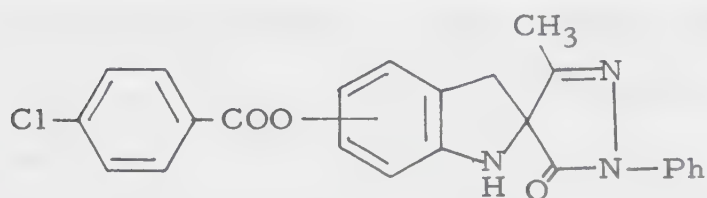
(373)

it displayed a molecular ion at m/e 431 which fragmented in a similar

way to the other substituted indoline derivatives (see later). In addi-

tion, acyl-oxygen fission occurred with charge retention on the acyl

portion (m/e 139); the latter fragmented further by the expulsion of a

CO molecule.

An attempt to hydrolyse this benzoyl derivative to the

corresponding phenol in order to help determine the position of sub-

stitution on the benzene ring failed to yield the required phenolic

compound.

iv. Reaction with p-toluenesulfonyl chloride:

Treatment of the N-hydroxyindoline (338) with p-toluene-

sulfonyl chloride in pyridine gave a yellow solid. When this solid was

dissolved in benzene, it deposited a crystalline compound which was

found to be the dehydrated product (A) obtained when (338) was reacted

with acetic anhydride (see p. 114). Evaporation of the remaining

filtrate produced a solid residue which was chromatographed on a

silica gel column, yielding two compounds. The major of these

compounds was identified as the spiro-(5-chloroindoline)pyrazolone

(346a) prepared earlier in this study. Direct comparison of the

physical properties of both (346a) and the major isolated product est-

ablished this identity. The minor product analyzed for $C_{24}H_{22}N_3O_4S$

and its mass spectrum displayed a molecular ion at m/e 447 which

supports this formula. This, however, was not an N-tosyloxy deriva-

tive since the i.r. spectrum demonstrated a broad absorption band

centered at 3340 cm^{-1} (NH). The n.m.r. spectrum also showed, in

addition to the methyl, methylene and aromatic signal, a D-exchange-

able one-proton signal at δ 5.0. These data suggested that the

initially formed N-tosyloxy derivative rearranged to an isomeric

tosylate which was assigned structure (374). The position of the

tosylate group was not determined due to the complexity of the aromatic

signal in the n.m.r. spectrum.

(374)
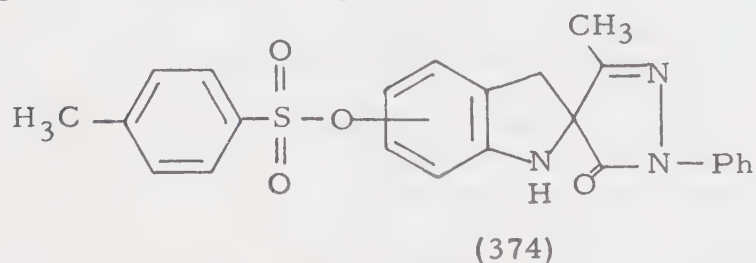
In another attempt to isolate an N-tosyloxy derivative,

the reaction of (338) and tosyl chloride was performed in ether at $0°$,

in the presence of triethylamine. A black semisolid resulted which

was shown by thin layer chromatography to contain at least five

components. This was not investigated further.

f) Methylation:

An attempt to react the spiro (1-hydroxyindoline)pyrazolone

(338) with diazomethane, in the absence of any catalyst, failed to yield a methoxy derivative. When this reaction was carried out in methanol using boron trifluoride as catalyst, it produced a crystalline product which was found to be the 5-methoxyindole (346b). This compound resulted from an acid-catalyzed nucleophilic attack, by methanol, on the ring carbon. Accordingly, it was realized that this reaction should be performed in a medium free from alcohol. The reaction was repeated in dioxane and alcohol-free diazomethane and boron trifluoride-ether complex were used. This produced a dark-green product, the i.r. spectrum of which displayed a C=O absorption band at 1720 cm^{-1} but no OH or NH absorption. When this product was dissolved in cold ethanol, a high-melting solid (309°) slowly separated. This compound analyzed for $C_{17}H_{13}N_3O$ (M^+ = 275) and gave i.r. and mass spectra which were virtually identical to the dehydrated product (A) obtained when the N-acetyloxy compound (349) was treated with ethanol (see p. 114). A mixed melting point of both compounds showed no depression. The formation of this dehydrated product during crystallization of the crude product suggested that O-methylation did occur, then the methyloxy derivative decomposed and/or rearranged. Such a rearrangement could be catalyzed by traces of acid present with the crude product. Some support for this suggestion is the fact that it was possible to obtain the desired N-methoxyindoline (375) by methylating (338) with methyl iodide in the presence of sodium methoxide.

(375)
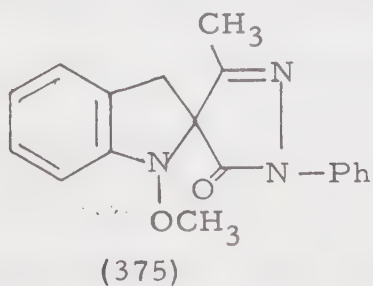
Identification of this compound was based on its elemental analysis ($C_{18}H_{17}N_3O_2$) as well as its i.r. ($\nu C=O$ at 1719 cm^{-1}) and n.m.r. (N-OCH_3 at $\delta 3.8$) spectra. The mass spectrum of this compound (part IIIb) was also very informative; it displayed a molecular ion at m/e 307 and a strong $(M-31)^+$ ion resulting from the expulsion of a $CH_3\dot{O}$ radical from the molecular ion. The expulsion of this fragment is not normally observed in the mass spectra of methyl ethers unless an ortho-effect operates (Cable et al, 1972; Coutts and Malicky, 1973).

Other Reductions of 4-(2-Nitrobenzyl)-2-pyrazolin-5-ones (319a,b,c).

a. Reduction with iron and ferrous ammonium sulfate:

Aromatic nitro compounds are known to be readily reduced to amines by this reducing system (Hodgson and Hathaway, 1944; Hickinbottom, 1959). Reduction of the nitrobenzyl derivative (319b) using this method yielded the 4-(2-aminobenzyl)pyrazolone (321b). In contrast, reduction of the methyl analog (319a) was unpredictable. It sometimes gave the spiro-(N-hydroxyindoline)pyrazolone (338); on other occasions it yielded the 4-(2-aminobenzyl)pyrazolone (321a) or a mixture of both products. Varying the reduction time did not improve the situation. It is suggested that differences in the batches of iron used could account for these variable results.

b. Reduction with zinc and ammonium chloride:

This is generally a standard procedure for the reduction of aromatic amines to the corresponding hydroxylamines. Mousseron-Canet and Boca (1965) used this system to reduce some o-nitrobenzyl ketones to substituted 1-hydroxyindoles. When this reaction was performed with the 4-(2-nitrobenzyl)pyrazolone (319a), no N-hydroxy

derivatives were obtained. The reaction yielded the spiro(indoline) pyrazolone (339) in poor yield. Reduction of the phenyl analog (319b) with the same reagent gave the corresponding spiro(indoline)pyrazolone (343) in good yield. In contrast, the 4(5-chloro-2-nitrobenzyl) pyrazolone (319c) gave a mixture of the spiro(5-chloroindoline)-pyrazolone (345a) and the corresponding N-hydroxyindoline (347).

c.   Reduction with zinc and acetic acid:

Heating the nitrobenzyl derivative (319a) with zinc and acetic acid gave a dark yellow product which melted at 166-8° and proved difficult to purify. The i.r. spectrum lacked NH, OH and C=O absorption bands which suggested a pyrazoloquinoline derivative (376a). This suggestion was supported by the absence, in the n.m.r. spectrum of this compound, of any signals other than those of the methyl group and aromatic protons. Its mass spectrum displayed a molecular ion at m/e 259 which fragmented mainly by the expulsion of a hydrogen atom, a methyl radical and a methyl cyanide molecule (Scheme 14). A literature search revealed that this compound (376a)
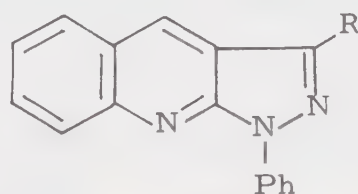
a, R=CH$_3$

b, R=Ph

(376)

was known (m.p. 178°) having been prepared by heating the Schiff base of 4-formyl-3-methyl-1-phenylpyrazole and aniline (Brack, 1962).

When the phenyl analog (319b) was reduced with zinc and acetic acid, it yielded a pure yellow crystalline compound, C$_{22}$H$_{15}$N$_3$,

which had i.r. and n.m.r. spectra very similar to those of (376a).
The mass spectrum of this compound had a strong molecular ion of
m/e 321 which was in agreement with the hitherto unknown structure
(376b). Other than the molecular ion, this mass spectrum had only
three ions of appreciable intensity resulting from the expulsion of a
hydrogen atom, a phenyl radical and a phenyl cyanide molecule from
the molecular ion (Scheme 14).

(376), M‡

$-RCN$ \quad * \qquad $-R^{\cdot}$ \qquad * \quad $-H^{\cdot}$

$[C_{15}H_{10}N_2]^{\ddagger}$
m/e 218

$[C_{16}H_{10}N_3]^{+}$
m/e 244

$[RC_{16}H_9N_3]^{+}$
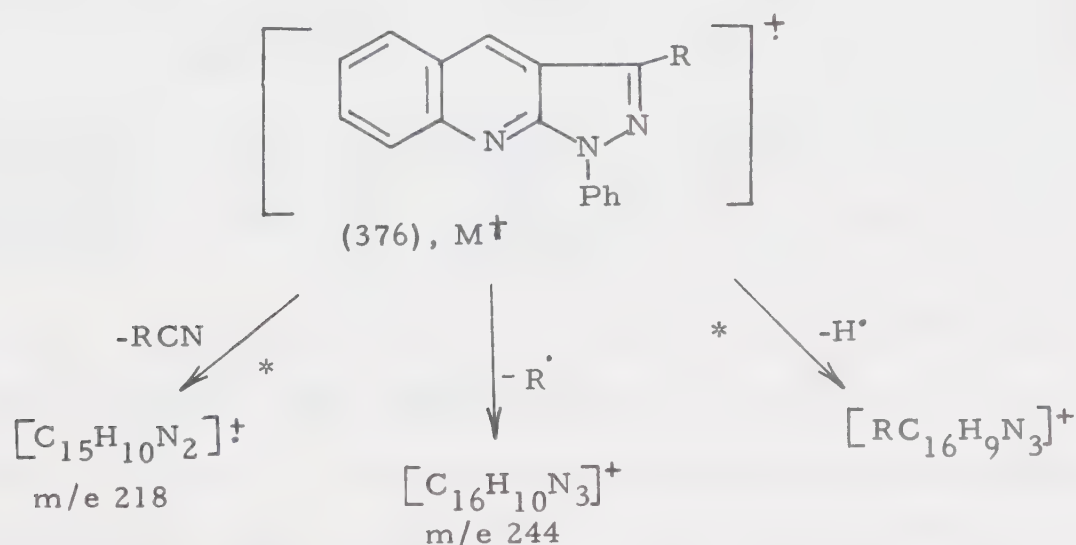
Scheme 14

Both these compounds (376a and b) were also obtained by
heating the amines (321a, b) with acetic acid for several hours.

d. Catalytic hydrogenation: Preparation of some spiro-(tetrahydro-
quinoline)pyrazolones (337).

Catalytic hydrogenation of o-nitrobenzylpyrazolone
derivatives (319a and b) was attempted to determine whether N-hydroxy
compounds could be obtained by this route. During one of these trials,
an interesting reaction was revealed. Catalytic reduction of two
o-nitrobenzylpyrazolones (319a and b) was carried out using platinum
oxide or palladium-charcoal as a catalyst and absolute ethanol as
solvent. 1-Methyl-4-(2-aminobenzyl)-3-phenyl-2-pyrazolin-5-one

(321a) was the main product isolated from the reduction of the 3-methyl-pyrazolone (319a), but when the related 3-phenylpyrazolone (319b) was reduced under the same conditions, a different type of product was obtained. This product (designated compound B) was weakly basic and, unlike (321b), was insoluble in dilute sodium hydroxide solution.

$$H_2/cat.$$ EtOH

(319a)   (321a)

$$\xcancel{H_2/cat.}$$ EtOH

$$H_2/cat.$$ Dioxane

(319b)   (321b)
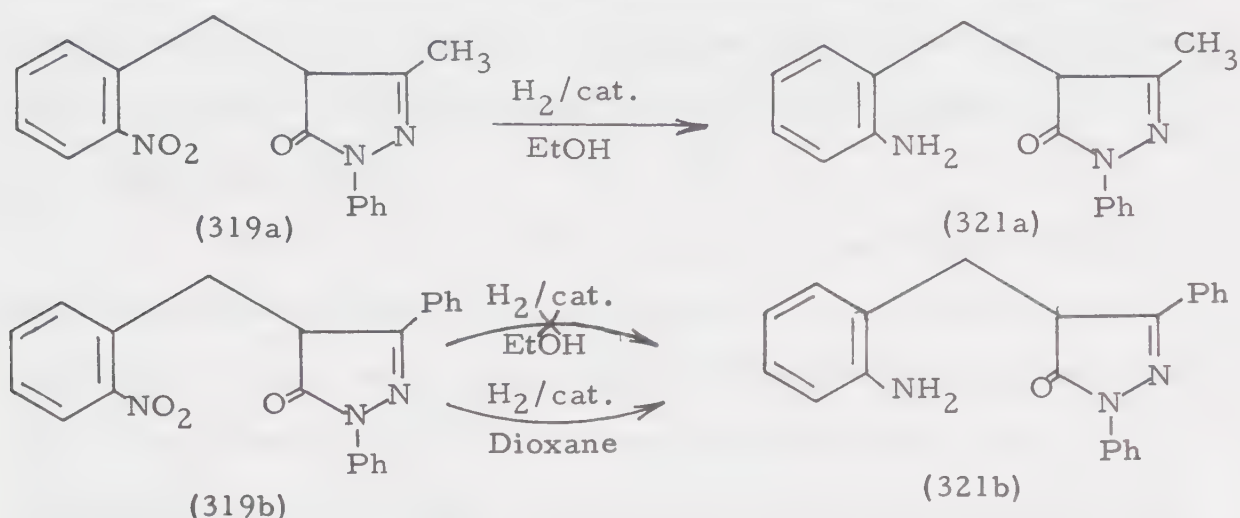
Its i.r. spectrum had an NH absorption band at 3405 cm^{-1} and a C=O band at 1712 cm^{-1}. The presence of a carbonyl absorption at this frequency in addition to the lack of solubility of product (B) in dilute alkali solution, indicated that the pyrazolone ring was no longer capable of enolization i.e. the hydrogen atom α to the C=O group was no longer present. The n.m.r. of compound (B) included a 3-proton doublet centered at δ1.15 (J=6.5 Hz) and a one-proton quartet signal centered at δ3.6 (J=6.5 Hz). This n.m.r. evidence, therefore, revealed the presence of a $-\overset{\mid}{C}H-CH_3$ group in the product which apparently originated from the ethanol employed as the solvent in the catalytic reduction of (319b). To see if that was the case, the same reaction was repeated in dioxane, in methanol, in propanol and in benzyl alcohol. With dioxane, 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b) was obtained in good yield, but when the other

solvents were employed, the products obtained in each case differed, and elemental analyses suggested that the alkyl or aryl group of the alcohol used had been incorporated into the molecule. The i.r. spectra of all these products were very similar but their nuclear magnetic resonance spectra confirmed differences in the structures of the products. The mass spectra of these derivatives were recorded and proved without doubt that the alcohols used as solvents were involved in this reaction.

From all these data, the general structure of compound (B) and the three related products was suspected to be the spiro-tetra-hydroquinoline derivatives, spiro [(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(2'-substituted-1',2',3',4'-tetrahydroquinolines)] (377). A mechanism for the formation of these spiro-tetrahydroquinolines (377) can be envisaged and is illustrated in Scheme 15. The nitro compound (319b) is reduced to the hydroxylamine (378) which then interacts with the alcohol present; the former is reduced to the amine (321b) while the latter is oxidized to the aldehyde. Both the amine and the alde-hyde react to form a carbinolamine (or aldol) (379) which cyclizes to the tetrahydroquinoline derivatives (377). This suggested oxidation-reduction process, and subsequent interaction of the products, is another example of solvent/product interactions known to occur during catalytic hydrogenation (Pylander, 1967).

Some other structures for the unexpected reduction products were considered. Among these, the isomeric imines (Schiff bases) (380) had first consideration. It is known that aldehydes and ketones add to the primary amines, and this addition involves nucleophilic attack by the basic nitrogen at the carbonyl carbon atom

Scheme 15

a , R = H

b , R = CH₃

c , R = C₂H₅

d , R = Ph
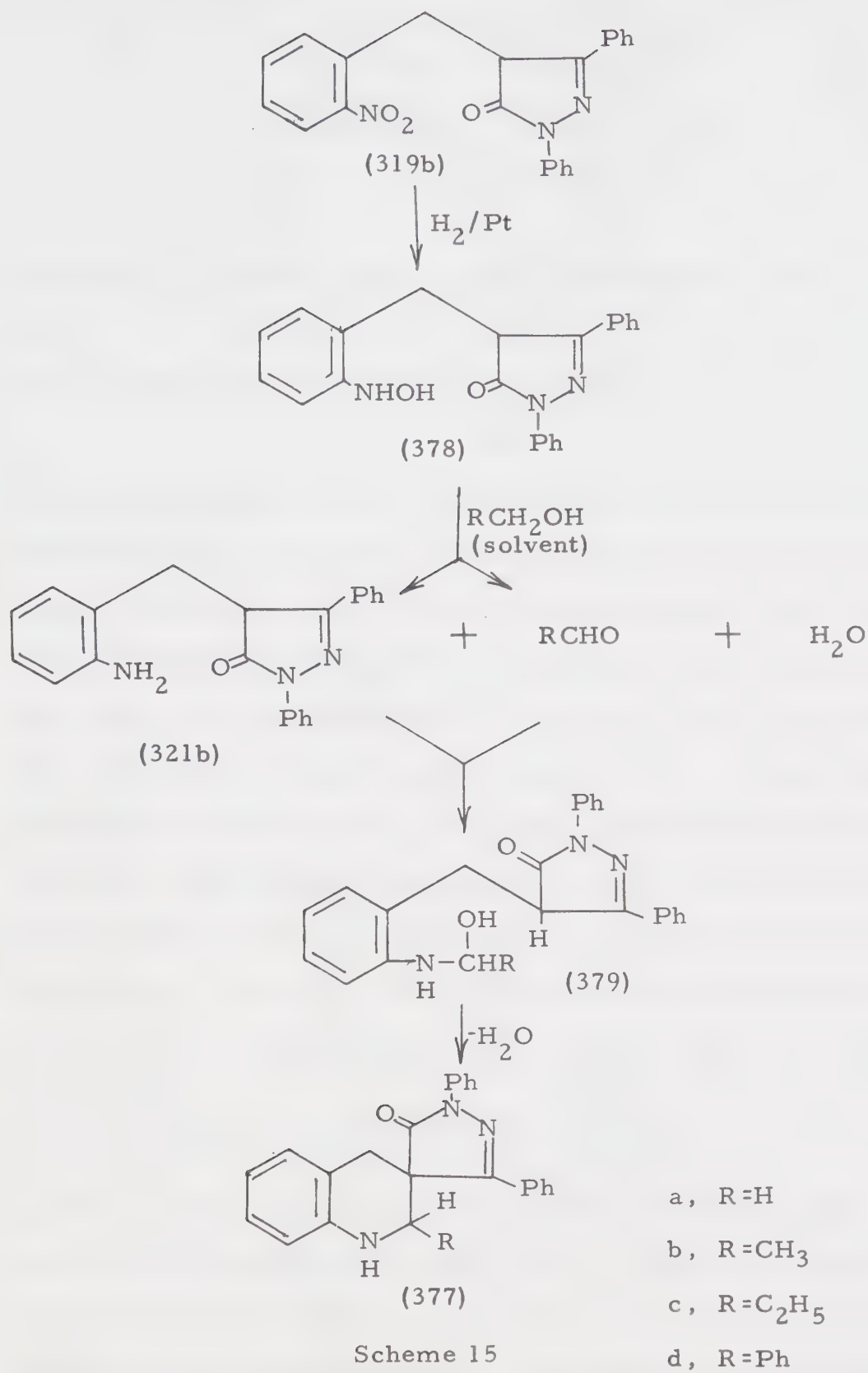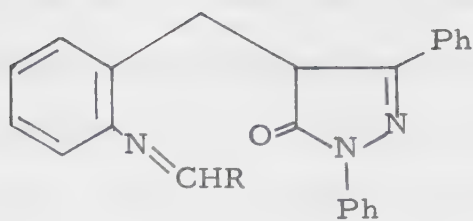
$$\text{(380)}$$

(equation 1). In most cases, the first step is the formation of an aldol

$$RNH_2 + R'R''C=O \rightleftharpoons \left[\begin{array}{c} H \quad OH \\ | \quad\; | \\ R-N-C-R' \\ | \\ R'' \end{array} \right] \rightleftharpoons RN=CR'R''+H_2O \quad (\underline{1})$$
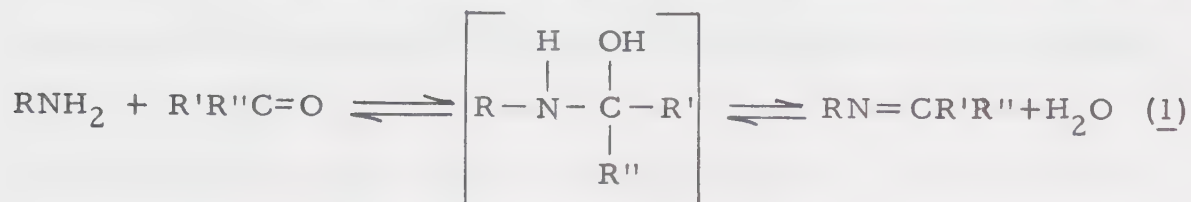
or ketol, but in the majority of cases, the carbinolamine intermediate

is unstable and not isolated. It reacts further in one of several ways,

the most common of which is the elimination of water to give the imine.

The possibility of compound (B) possessing an imine structure (380)

was ruled out by an analysis of the i.r., n.m.r. and mass spectra as

well as by the chemical properties of the product. The presence of

N–H stretching bands in the i.r. spectra of all four compounds (377,

$R = H$, CH_3, C_2H_5 and Ph) is incompatible with the imine structure.

A broad deuterium-exchangeable signal in the n.m.r. spectrum was

also observed. In imines, an NH absorption can be present if they

exist in the enamine form (equation $\underline{2}$). Imines with α-hydrogens are

$$R-N=C-CH_2R'' \rightleftharpoons R-N-C=CHR'' \qquad (\underline{2})$$

with R' on the first carbon and R' on the second carbon; the second structure has H on N.
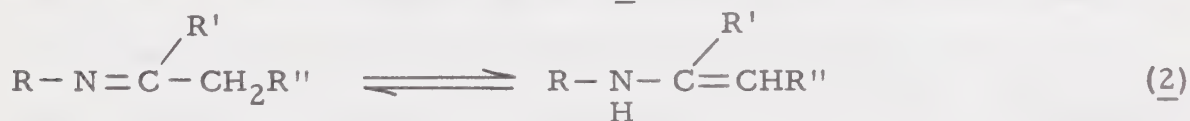
capable of imine-enamine isomerism similar to the keto-enol tautomer-

ism of carbonyl compounds (Layer, 1963). This type of isomerism

was clearly demonstrated in a number of cases, but Witkop (1956)

found no evidence for the presence of the enamine structure in his

i.r. studies. Conclusive evidence that the compounds obtained, when

(319b) was reduced in various solvents, did not have the imine struc-
ture came from a consideration of the product obtained by hydrogen-
ation of (319b) in benzyl alcohol. This product gave rise to an NH
stretching band in the i.r. spectrum despite the fact that it had no
α-hydrogen capable of imine-enamine isomerization.

Further evidence for the suitability of structure (377) was
obtained from an analysis of the mass spectra of the four compounds
(377, R=H, CH_3, C_2H_5 and Ph). None of these fragmented under
electron impact in the manner that Schiff bases do. Mass spectral
studies of some Schiff bases have recently been reported by Elias and
Gillis (1966). They showed that the molecular ion undergoes simple
fission at the ring-nitrogen and ring-carbon bonds; the former frag-

$$R \underbrace{}_{} N = CH \underbrace{}_{} R'$$
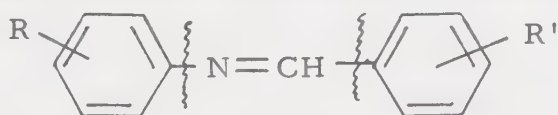
mentation is more facile than the latter. No fragment ions due to ring-
nitrogen fission were present in the mass spectra (Fig. 6 and 7) of
any of the products isolated. On the other hand, the fragment pattern
observed followed the behavior of tetrahydroquinoline derivatives under
electron impact (Draper and MacLean, 1968) (Scheme 16, p. 148).

A final argument against the imine structure (380) was
based on the fact that such a structure should not be isolated under
such reduction conditions. Schiff bases are known to be reduced in
virtually quantitative yields either by catalytic hydrogenation or by
chemical reagents (Adkins, 1937), and accordingly, the imine if it
were formed would be reduced to the secondary amine (equation 3).

$$R-N=CR'R'' \xrightarrow{H_2} R-\underset{H}{N}-\underset{H}{C}-R'R: \tag{3}$$

However, the imine is thought to have a transitory existence in the

formation of these tetrahydroquinoline derivatives (377). Two

possible mechanisms can be suggested for the cyclization stage. It

is possible that the aldol (379) dehydrates directly to give the tetra-

hydroquinoline (377):

(379)   (377)
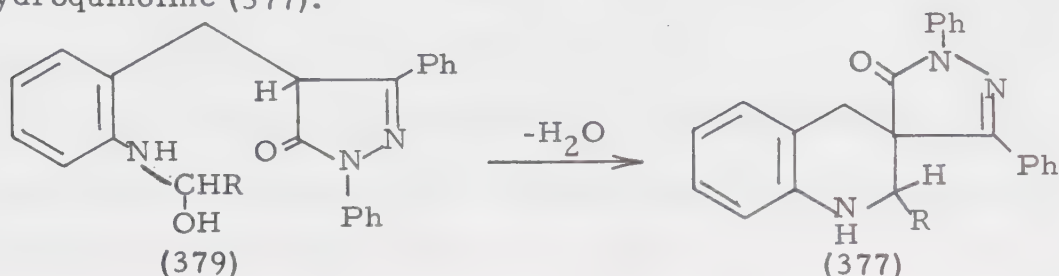
Alternatively, the aldol could dehydrate to form the Schiff base (380)

which then cyclizes:

(380)
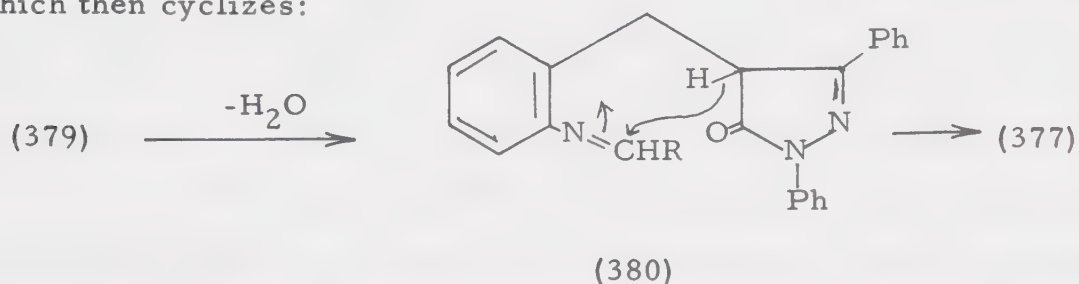
The Schiff base intermediate mechanism is supported by the fact that

numerous compounds containing active hydrogens are known to add

readily to the imines in the following manner:

$$RN{=}CR'R'' \quad + \quad R'''H \longrightarrow R{-}N{-}CR'R''R''' \qquad (4)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad H$$

Catalysts such as aluminium chloride or cuprous chloride are often

required in this reaction (Layer, 1963). The pyrazolone derivatives,

1-phenyl-2,3-dimethylpyrazolin-5-one (antipyrine) and 1-phenyl-3-

methylpyrazolin-5-one are among the active hydrogen compounds

reported to add to Schiff bases (Passerini and Ragni, 1936). This is

due to the activity of the hydrogen atom at C-4 of the pyrazolone ring.

Antipyrene (329) was found to add to N-benzylideneaniline (381) when

both were dissolved in ethanol and left at room temperature for five

weeks. The product isolated was identified as 4-benzalanilantipyrene

(382).

(381)   (329)   (382) Ph
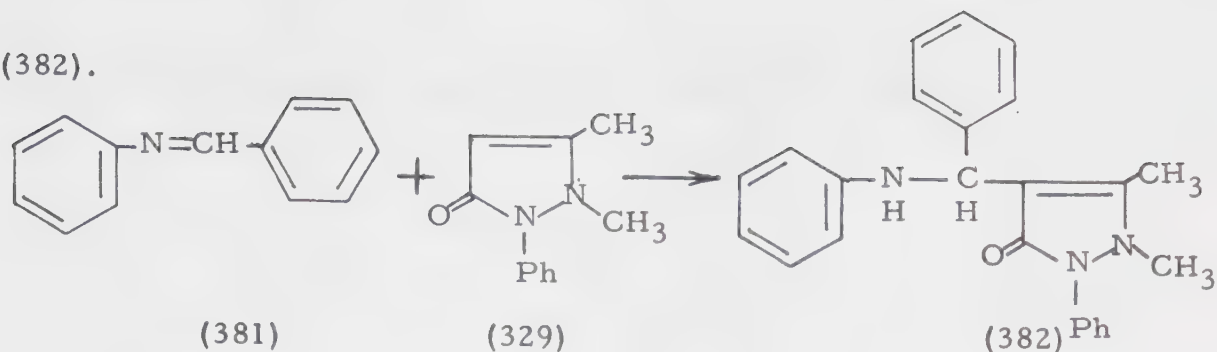
If the postulated mechanism depicted in Scheme 15 was factual, it should be possible to prepare numerous compounds of the general structure (337) in the manner shown:

(321a,b)   Ph   (337)
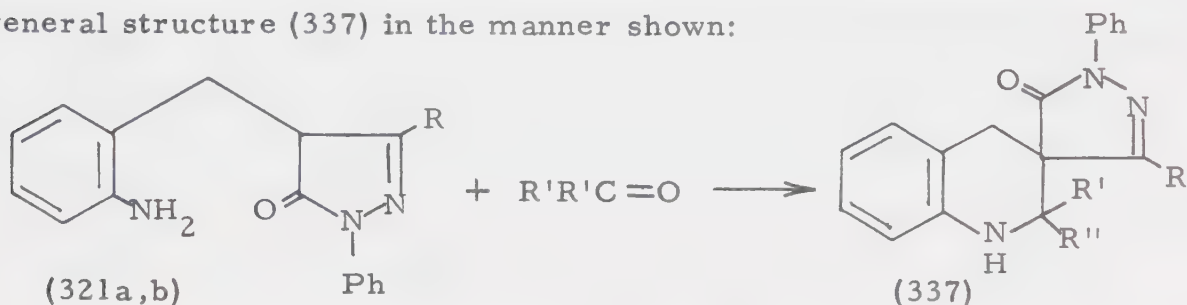
This proved possible. Eighteen spiro-tetrahydroquinoline derivatives (Table 2) were obtained from the amines (321a,b) and an appropriate aldehyde or ketone in refluxing ethanolic solution. The phenolic compounds (337d, e, f, g and o) and the carboxylic acid derivatives (337k and p) were prepared in particular because of their ability to dissolve in dilute alkaline solution, a property which was required to facilitate a planned pharmacological evaluation.

Aliphatic ketones are known to react with amines more slowly than aldehydes to form imines. This was the case here; it necessitated the use of higher reaction temperature and longer reaction times to obtain the tetrahydroquinoline derivatives (337q) and (337r) in the absence of catalyst or dehydrating agent. The reaction between (321a) and acetone required shorter reflux time when the solvent was butanol rather than ethanol. Attempts to crystallize the isolated product were unsuccessful but the i.r. and n.m.r. spectra of this

Table 2:   Spiro(tetrahydroquinoline)pyrazolone derivatives.

(337)
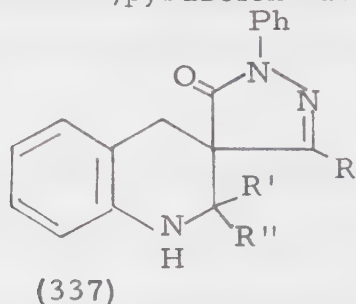
	R	R'	R''		R	R'	R''
a	CH$_3$	H	CH$_3$	k	CH$_3$	H	—C$_6$H$_4$—COOH
b	CH$_3$	H	C$_2$H$_5$				
c	CH$_3$	H	Ph	l*	Ph	H	CH$_3$
d	CH$_3$	H	—C$_6$H$_4$—OH	m*	Ph	H	C$_2$H$_5$
				n*	Ph	H	Ph
e	CH$_3$	H	—C$_6$H$_4$(OH) (ortho-OH)	o	Ph	H	—C$_6$H$_4$—OH
f	CH$_3$	H	—C$_6$H$_3$(OH)(OH)	p	Ph	H	—C$_6$H$_4$—COOH
g	CH$_3$	H	—C$_6$H$_3$(OCH$_3$)(OH)	q	CH$_3$	CH$_3$	CH$_3$
h	CH$_3$	H	—C$_6$H$_3$(OCH$_3$)(OCH$_3$)	r	Ph	CH$_3$	CH$_3$
i	CH$_3$	H	—C$_6$H$_4$—NH$_2$				
j	CH$_3$	H	—C$_6$H$_4$(NH$_2$) (ortho-NH$_2$)				

*   These compounds are included in the table for completeness but are previously discussed under the identification numbers 377b, c and d.

product agreed with the proposed structure. The reaction between
the phenyl analog (321b) and acetone was more facile and the product
was easily characterized.

When the amines (321a, b) were reacted with formaldehyde,
they failed to form the spiro-tetrahydroquinoline derivatives (383).
The crystalline product obtained from heating (321b) with formalde-
hyde solution in ethanol analyzed incorrectly for the required com-
pound. The i.r. spectrum of the product had a carbonyl band at 1711
cm^{-1} and no NH or OH absorption. It remains unidentified. The
same reaction repeated with the methyl analog (321a) failed to yield
any crystallizable products. The required spiro-tetrahydroquinolines
(383) were readily obtained, however, when the nitro compounds
(319a, b) were catalytically hydrogenated over platinum using methanol
as a solvent.

(383)

a, R=CH$_3$

b, R=Ph
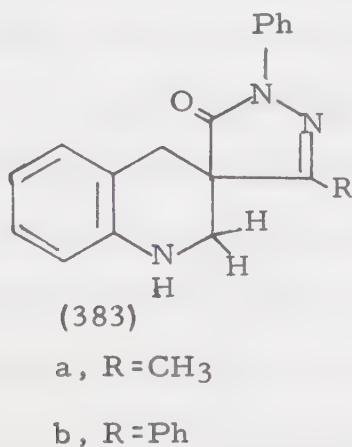
As a result of the successful formation of the tetrahydro-
quinoline (383a) by catalytic hydrogenation of (319a) in methanol, the
same reduction in ethanol was reinvestigated. It was found earlier
that this reaction yielded only the amine (321a). However, leaving
the reaction mixture for a further 24 hours at room temperature
resulted in the formation of the tetrahydroquinoline (337a) along with
the amine (321a). Separation of both compounds depended on the

solubility of the latter in dilute sodium hydroxide solution.   A mixture

of the related tetrahydroquinoline (337b) and the amine (321a) was also

obtained when the same reduction was repeated in propanol.

All the tetrahydroquinoline derivatives prepared in this

study were identified by their correct elemental analysis and by the

similarities between their i.r. and n.m.r. spectra and those described

earlier for compounds (377a-d).   The mass spectra of some of these

derivatives were also recorded (Figs. 6 and 7) and some of the

possible fragmentation pathways are suggested in Scheme 16.

Deuteration of compound (337c) as well as recording of the spectrum

of the 2,2-dimethyltetrahydroquinoline (337r) were helpful in account-

ing for the origin of some of the fragment ions.   Each compound

demonstrated a strong molecular ion which was, in most cases, the

strongest in the spectrum.   The expulsion of a hydrogen atom as well

as the substituent (R') in the form of a radical from C-2 of the tetra-

hydroquinoline ring gave rise to weak fragment ions.   Exceptions to

that are those compounds having no substituents at C-2 (383, R'=H)

and those having aliphatic substituents (383, R'=CH_3 or C_2H_5) where

the (M-H) and (M-R') ions were found to be relatively strong.   Deuter-

ium labelling of (337c) showed that the hydrogen atom expelled in the

formation of ion a did not originate from the N-1 position of the tetra-

hydroquinoline ring.   The absence of this ion a in the spectrum of the

2,2-dimethyltetrahydroquinoline (337r) suggested that the hydrogen

atom at C-2 in the other compounds is the one involved.

An interesting fragment ion found in all the spectra

(except the dimethyl derivative 337r) was due to the expulsion of an

OH radical from the molecular ion.   That this expulsion is direct was

supported by metastable ions present at appropriate m/e values in most spectra. Deuterium labelling ruled out any contribution from the amine proton since the ion at m/e 450 in (337c) was located at m/e 451 in the deuterated compound. The absence of this ion in compound (337r) may suggest the involvement of the hydrogen atom at C-2 in the formation of the $(M-OH)^+$ fragment. However, without a detailed study it is not possible to make any deductions regarding the mechanism of OH loss. A similar fragment ion was detected in the spectra of the spiro-(indoline)pyrazolone derivatives (general structure 430) and a tentative mechanism for its formation was suggested in that instance (see Part III A).

Strong fragmentation ions ($\underline{d}$ and/or $\underline{d}'$) were present in the spectra of all compounds. These resulted at least in part, from the expulsion of a pyrazolone radical from the molecular ions as suggested by the presence of appropriate metastables. Depending on which hydrogen in involved in the expulsion of the pyrazolone radical, the two structures ($\underline{d}$ and $\underline{d}'$) are suggested for the ion formed. It seems, however, that the amine hydrogen is more involved in the proposed migration than the C_2-hydrogen. That was indicated by examining the spectra of both the deuterated compound (337c, N—D replaces N—H) and the 2,2-dimethyl derivative (337r). The former showed a major loss of 174 mass units from the molecular ion instead of 173 mass units lost in the non-deuterated compound (337c). The 2,2-dimethyl derivative (337r) molecular ion also expelled a pyrazolone radical (to give a fragment ion at m/e 146) thus implicating migration of the NH hydrogen atom, or alternatively, a hydrogen atom from the ring methylene group. Non-involvement of the protons at C-4 was
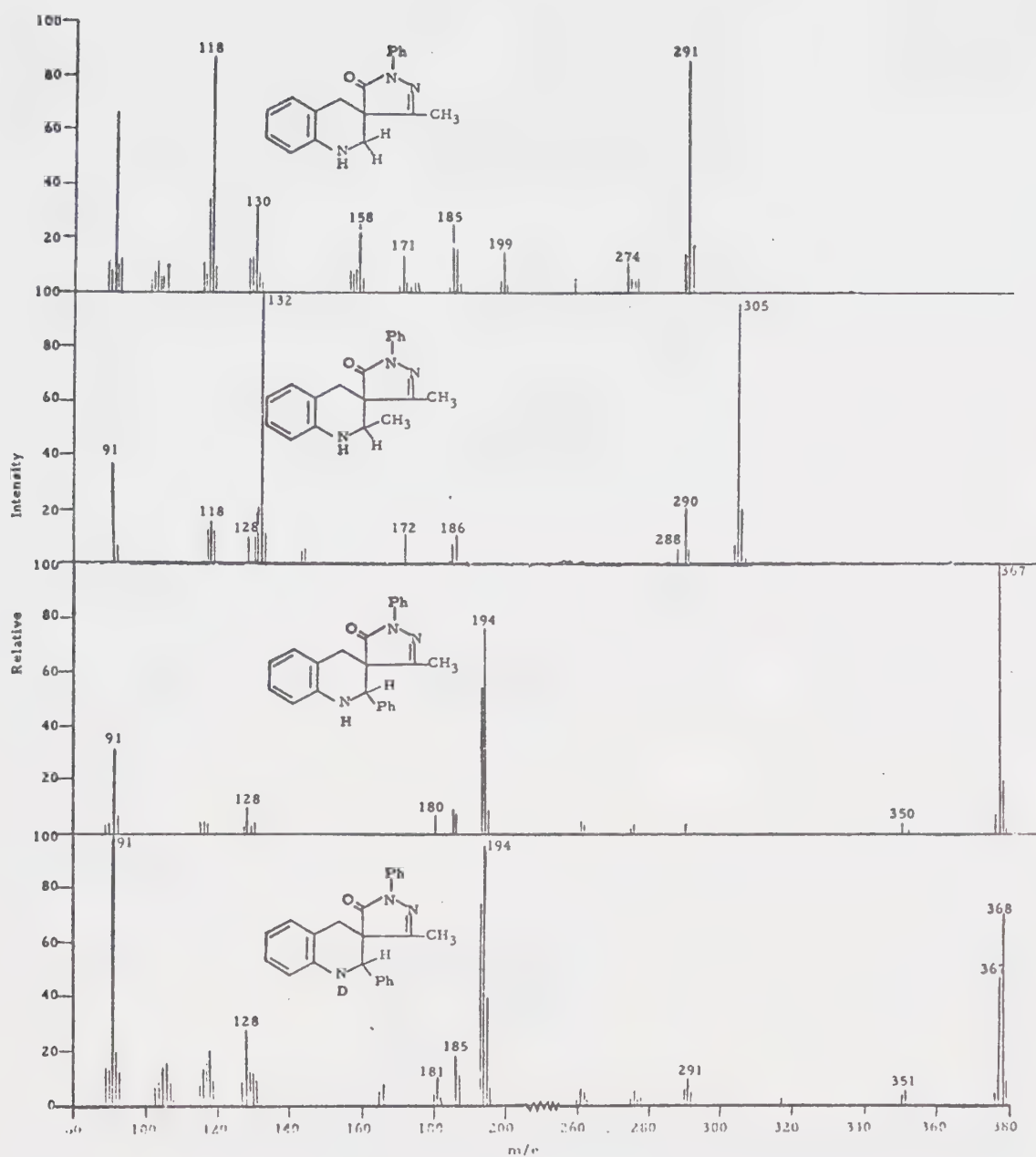
Fig. 6: Portions of the mass spectra of the spiro(tetrahydroquinoline) pyrazolones (383a, 337a, c) and the deuterated derivative of (337c).
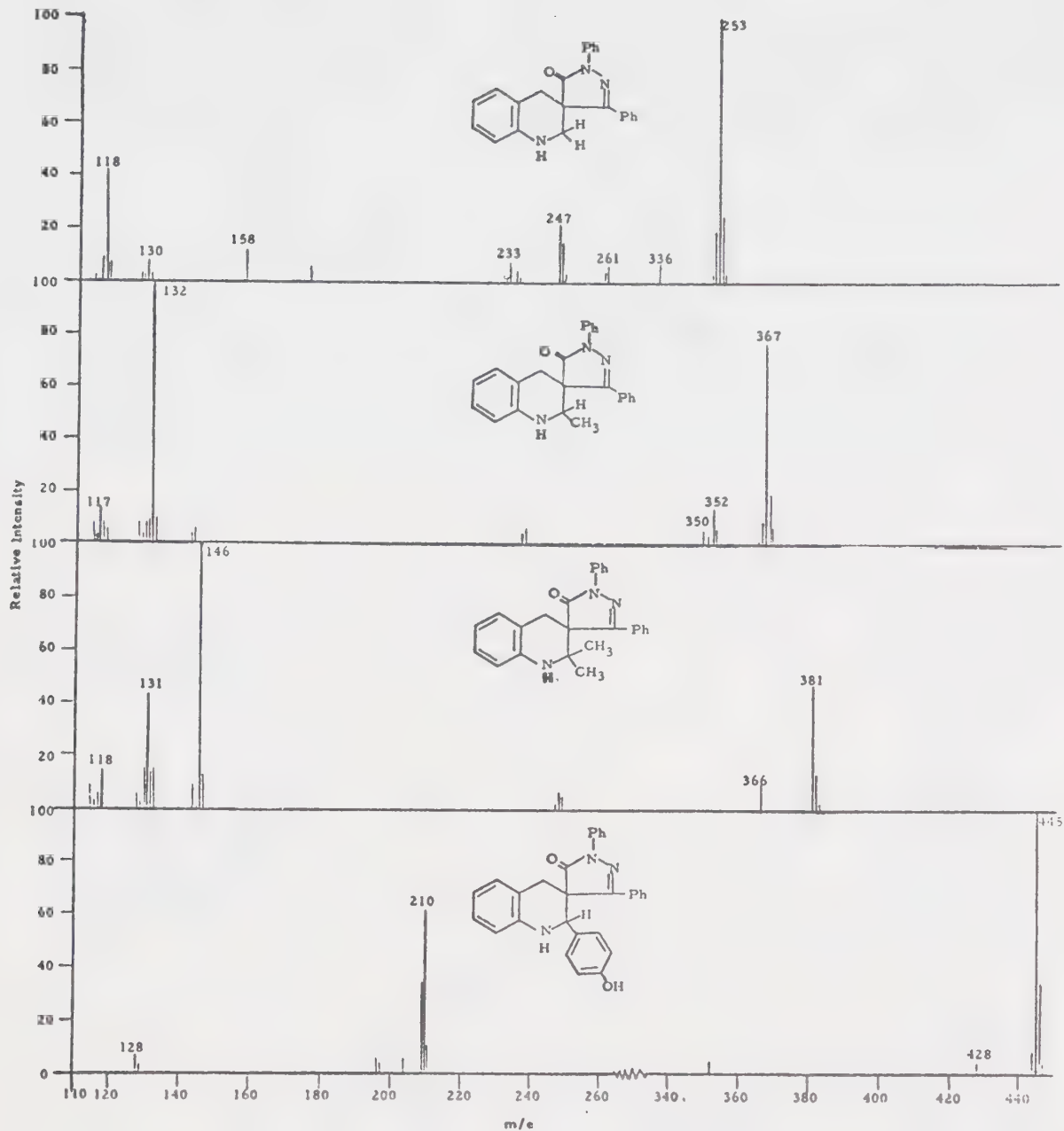
Fig. 7: Portions of the mass spectra of the spiro(tetrahydroquinoline)-pyrazolones (383b, 3371, r, o).
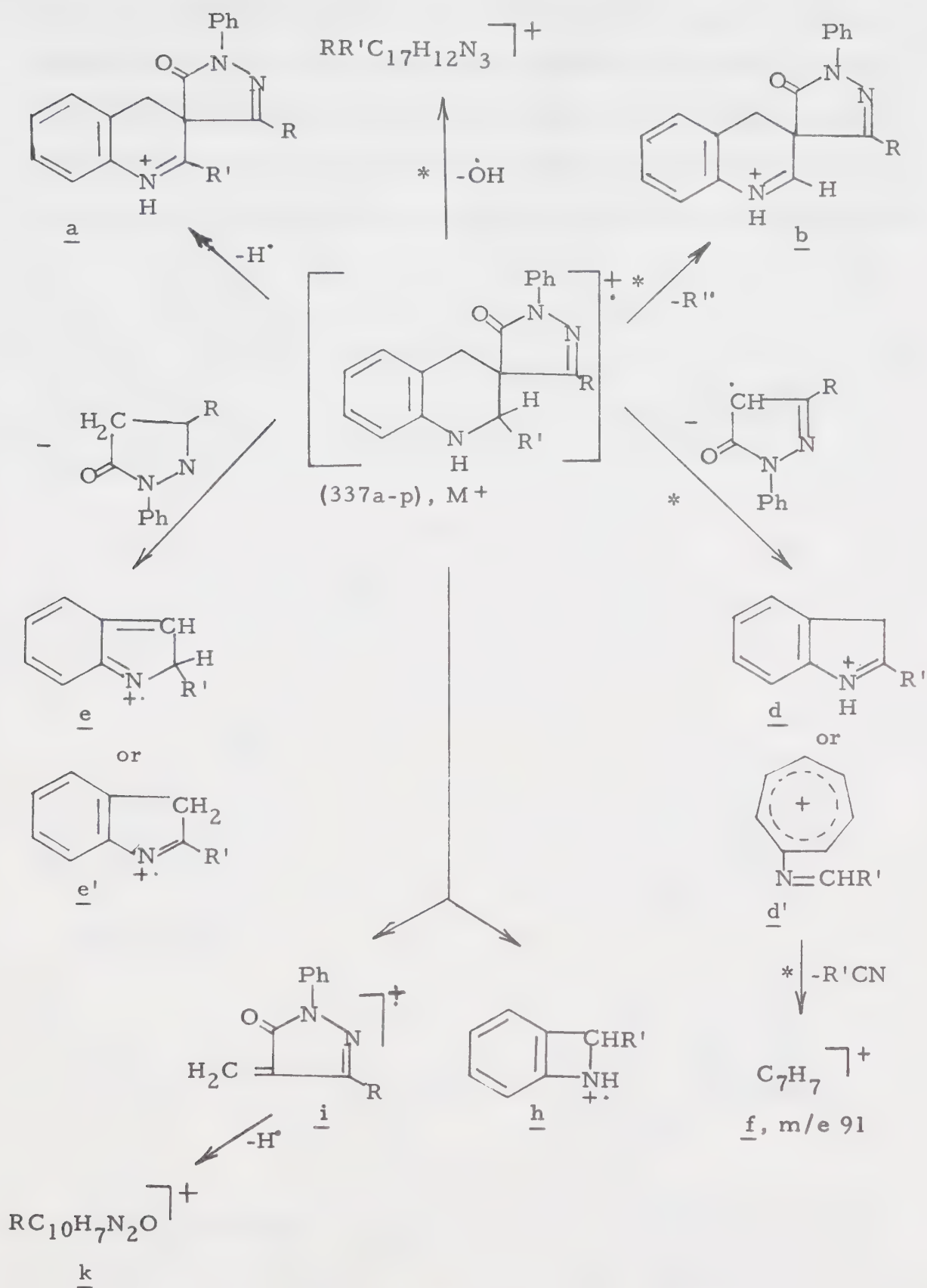
Scheme 16

suggested, however, by the presence of similar strong ions (d and d')
in the spectra of the spiro-dihydrobenzothiazines (see later) in which
the methylene group is replaced by a sulfur atom. A mechanism for
the formation of both ions d and d' is suggested in Schemes 17 and 18
respectively, but the latter is preferred for the reasons just expounded.

Scheme 17

Scheme 18
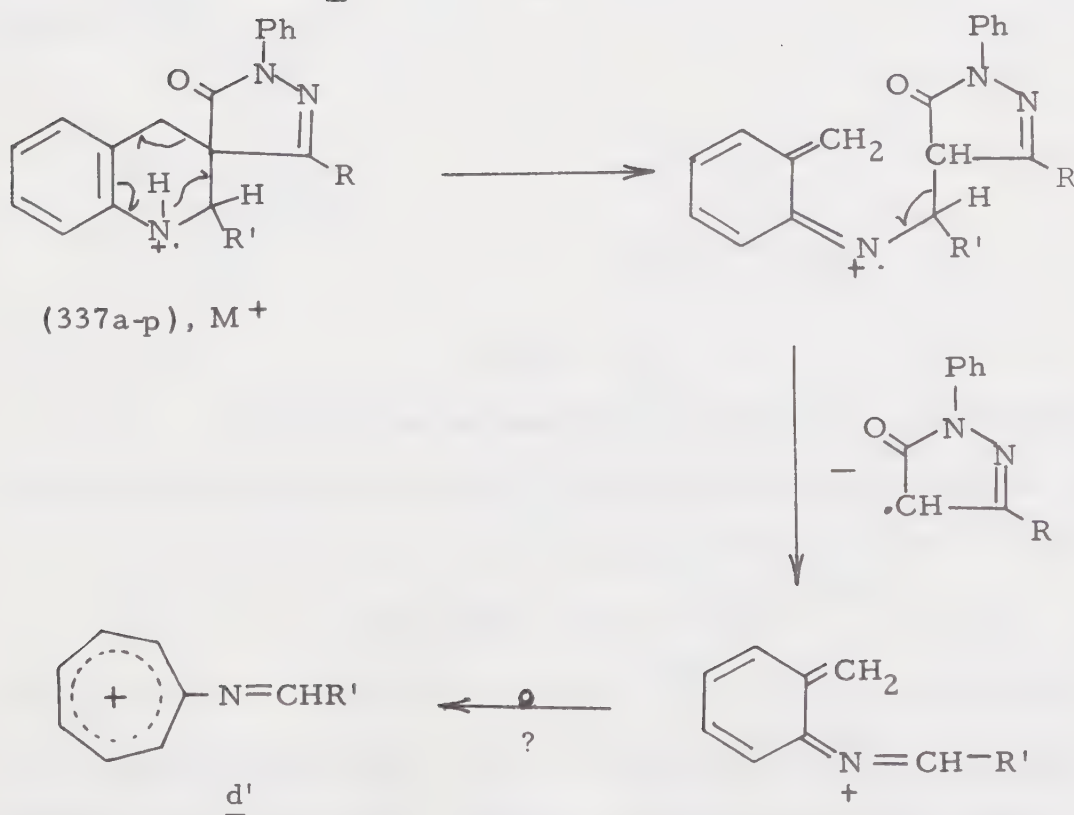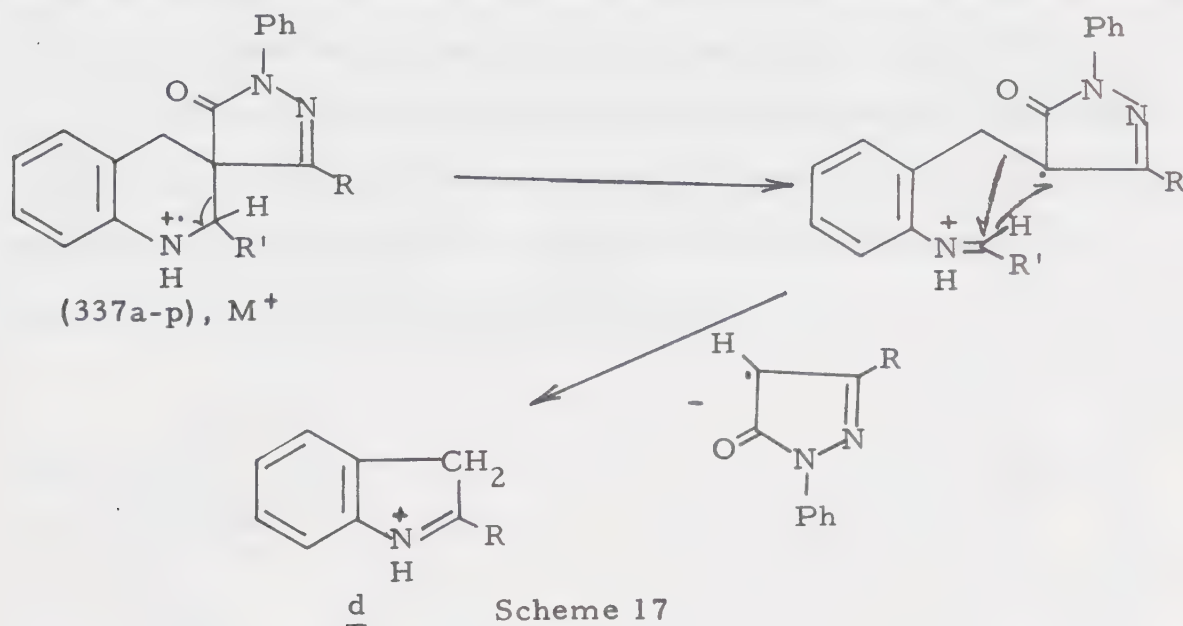
Another major pathway, especially in those tetrahydro-quinolines which are not substituted at C-2, is the decomposition of the molecular ion in two ways to give ions tentatively identified as h and i. The latter expells a hydrogen atom to give ion k for which no structure is proposed.

Another ion, which is represented in Scheme 16 as e or e', is present in relatively high abundance in the tetrahydroquinolines possessing aromatic substituents at the C-2 position. The deuteration experiment confirmed that the amine hydrogen atom was the one expelled in the formation of this ion (Scheme 19).

(337a-p), M⁺
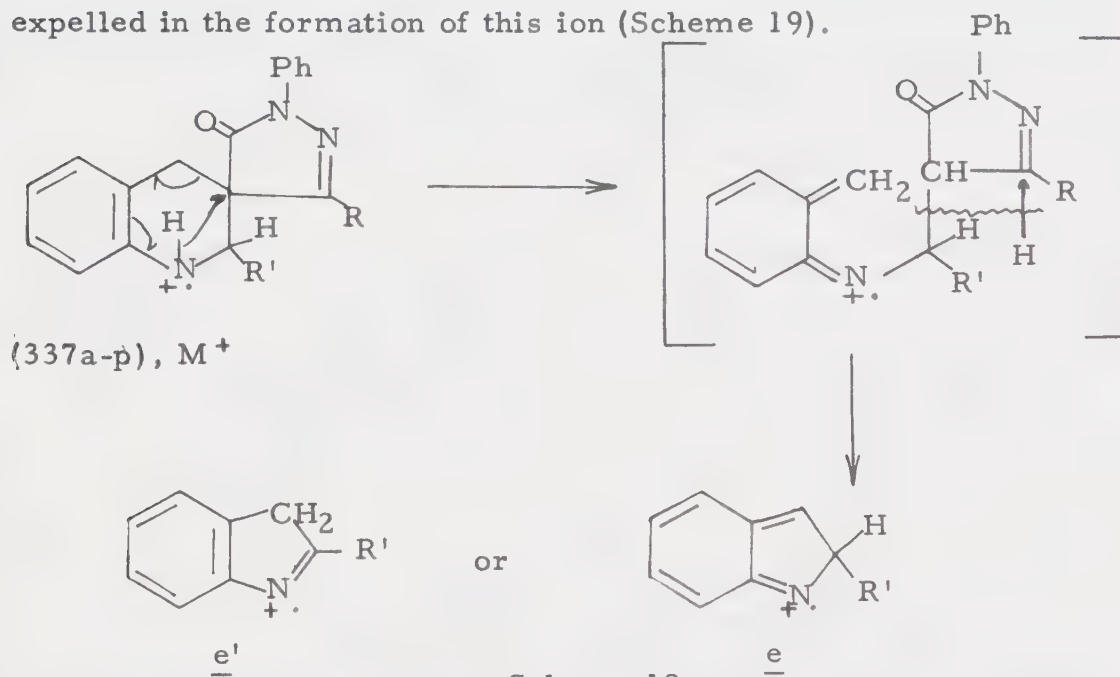
Scheme 19

A difference between the o-aminobenzylpyrazolone (321a) and its phenyl analog (321b) was demonstrated in their reactions with

(321)
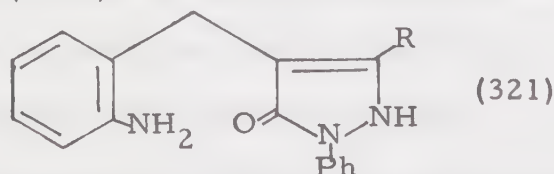
salicylaldehyde. Whereas (321a) was successfully converted to a spiro-tetrahydroquinoline (337e), the phenyl analog (321b) failed to produce such a structure. Instead, a yellow crystalline product

-designated as (C)-was obtained. It analyzed for $C_{29}H_{23}N_3O_2$ and had

an i.r. spectrum which was devoid of both the lactam $C=O$ and $N-H$

absorptions present in all the spiro-tetrahydroquinolines (337). The

spectrum contained a very broad absorption between 2100 and 3120

cm^{-1} in addition to four medium intensity bands at 1610, 1593, 1581

and 1568 cm^{-1}. These absorptions are comparable to those in the

i.r. spectrum of the Schiff base, salicylideneaniline (384) which was

prepared for comparison purposes. Accordingly, from these data,

the Schiff base structure (385) is suggested for compound (C).

(384)

(385)
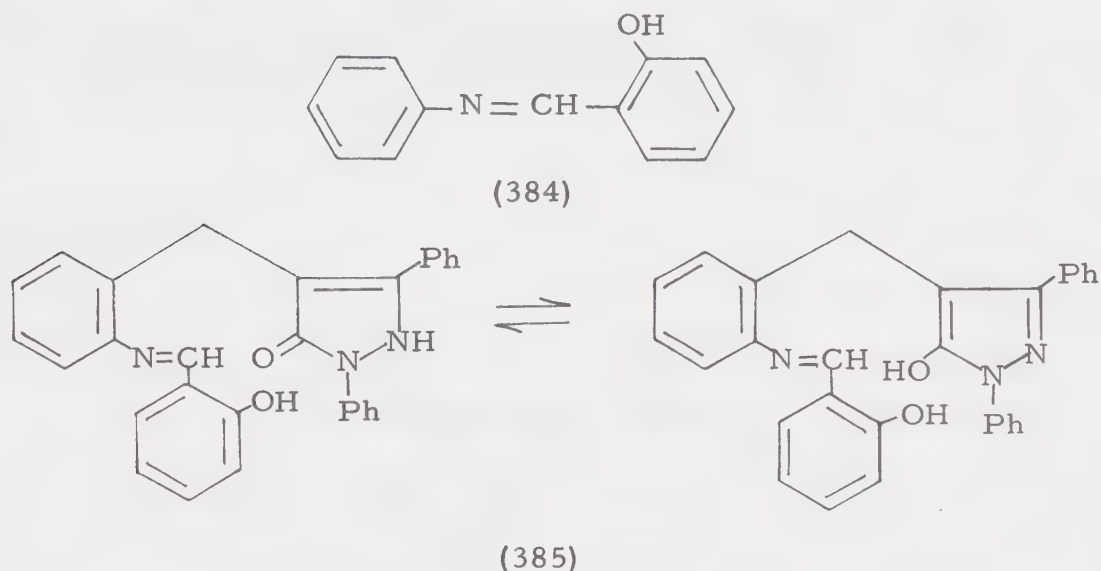
In addition to the elemental analysis and i.r. spectrum,

the mass spectrum of (C) was also in agreement with the proposed

structure. Although this spectrum (Fig. 8) displayed some similar-

ities with the spectra of the spiro-tetrahydroquinoline (337e), it also

showed strong fragment ions (Scheme 20) resulting from cleavage at ring

nitrogen or ring carbon bonds of the imine group. Both these fissions

were shown earlier (Elias and Gillis, 1966; Bowie et al, 1968) to

occur in the mass spectra of Schiff bases. When product C was

dissolved in DMSO-d_6 for an n.m.r. study, ring closure occurred.
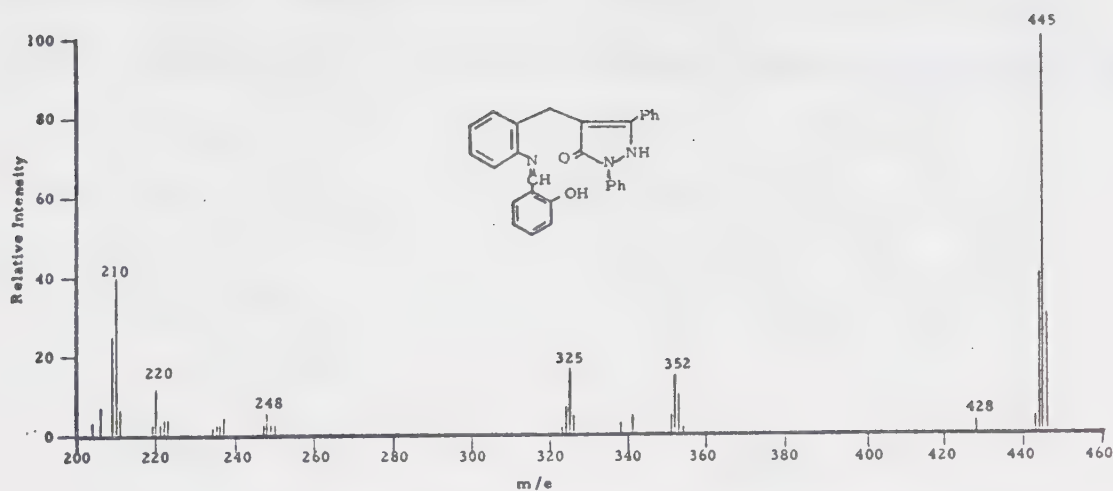
Fig. 8: A portion of the mass spectrum of 1,3-diphenyl-4-[2-(Q-hydroxybenzylidene)aminobenzyl]-2-pyrazolin-5-one (385).

Scheme 20
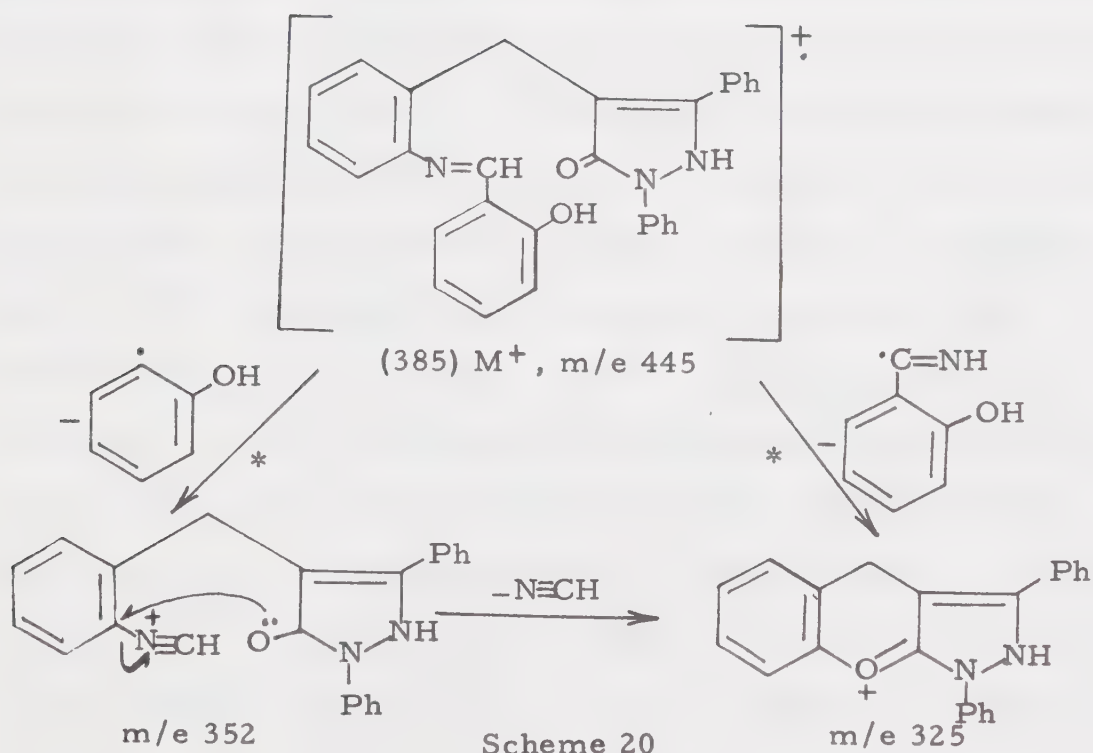
A spectrum very similar to that of the spiro-tetrahydroquinoline

(337o) was obtained. In particular, the spectrum of (C) displayed

a doublet of doublets for the methylene group. Such a signal was

demonstrated, throughout the present study, solely in spiro-compounds

such as (337e). Compound (385), therefore, is converted in the

n.m.r. solvent (DMSO-d_6) into the isomeric tetrahydroquinoline (386).

(337o)   (386)
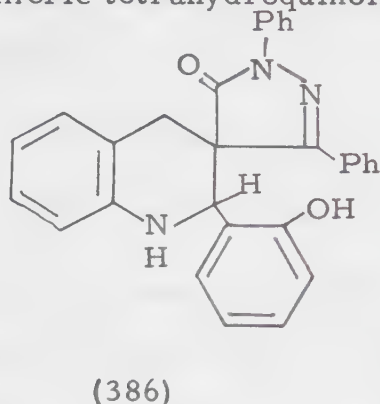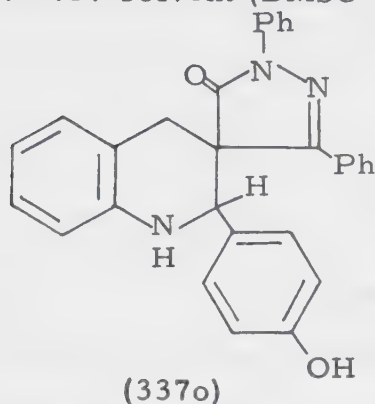
Reduction of (C) by means of sodium borohydride in

aqueous dioxane did not yield any crystalline product. Also, methyla-

tion with dimethyl sulfate gave an alkali-insoluble product which was

difficult to purify. The mass spectrum of the crude methylated product

displayed a weak molecular ion at m/e 473 which indicated a dimethyl

derivative in agreement with a Schiff base precursor (385) rather than

a tetrahydroquinoline (386), since in (385), methylation of the pyrazo-

lone nucleus, could also occur. As shown in the i.r. and mass

spectra of the isolated products, methylation occurred at the N-2

position of the pyrazolone ring. The i.r. spectrum displayed a $C=O$

at 1660 cm^{-1} which is expected only when the pyrazolone nucleus has

an α,β-unsaturated carbonyl group (Nakanishi, 1962). The mass

spectrum displayed, in addition to the M-1 and M-15 ions, a very

strong ion (the strongest in the spectrum) at m/e 118. A similar

ion was identified earlier (p. 89) in the mass spectrum of the N-2

methyl derivative (324b) as the fragment (Ph$-$C$\equiv$$\overset{+}{N}$$-CH_3$ $\longleftrightarrow$

Ph$-$$\overset{+}{C}$$=N-CH_3$). Accordingly, a structure (387) was assigned to the

dimethyl derivative obtained from (C).
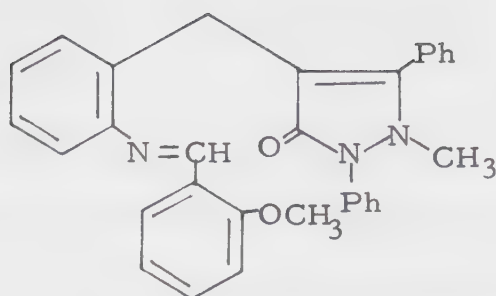
(387)

Acetylation of compound (C) with acetic anhydride pro-
duced a diacetate product (D) of molecular formula $C_{33}H_{27}N_3O_4$.
Three diacetylated structures (388), (389) and (390) are possible.
The O-5 position of the pyrazolone nucleus was found earlier to be
most susceptible to acetylation by acetic anhydride. However,
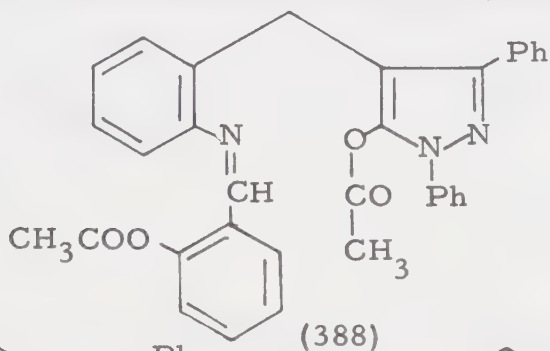
(388)
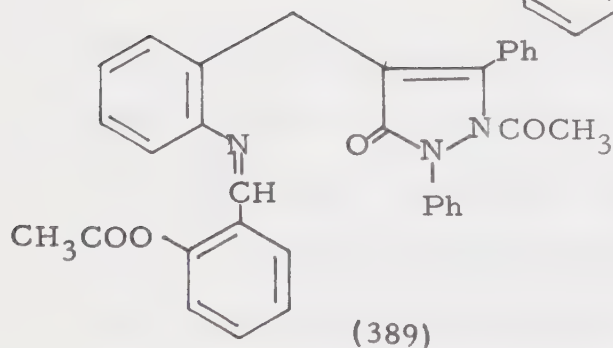
(389)
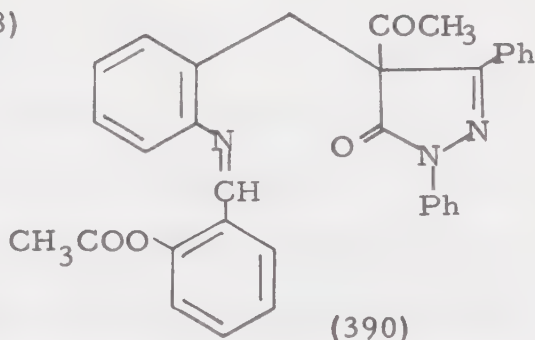
(390)

structure (388) was ruled out readily by examining the i.r. spectrum
of (D) which contained three carbonyl bands at 1764, 1720 and 1666
cm^{-1}. Compound (388), if it was formed, would show only two ester
carbonyl bands. The i.r. spectrum of (D) also disagreed with the
acetylated compound being (389) which is not expected to show C=O
absorption around 1720 cm^{-1}. Compound (390) is also a doubtful

possibility since the C=O stretching band at 1666 cm^{-1} is relatively low for a ketonic carbonyl.

The similarities in the i.r. and n.m.r. spectra of the isolated product (D) and a diacetate derivative (391) obtained by acetylation of an authentic tetrahydroquinoline (337o) suggested two related structures. The i.r. spectrum of (391) had three C=O absorption bands at 1765 (ester), 1715 (lactam) and 1668 cm^{-1} (cyclic amide) which are closely related to those in the i.r. spectrum of (D).
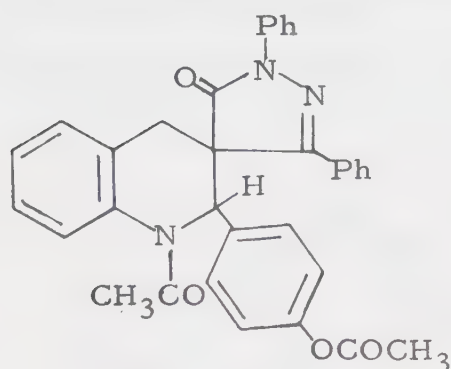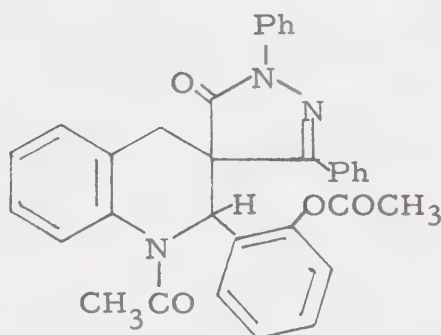
(391)   (392)

The n.m.r. spectrum of (391) displayed two methyl signals at δ2.1 (OCOCH$_3$) and at δ2.23 (NCOCH$_3$), a doublet of doublets centered at δ3.37 (CH$_2$) and an aromatic multiplet which included the C-2 proton signal. The corresponding signals in (D) were located at δ1.93, 2.24 and 3.26. These spectral similarities led to the assignment of cyclic structure (392) for the diacetate product (D).

Reactions of spiro-(tetrahydroquinoline)pyrazolones

(a) Acetylations: Acetylation of some other tetrahydroquinolines were attempted initially to compare the spectral characteristics of the products with those of compound D. The tetrahydroquinoline (337n)

yielded a monoacetyl derivative identified as (393). This structure

was confirmed by elemental analysis ($C_{31}H_{25}N_3O_2$), i.r. ($\nu_{C=O}$ at

1666 and 1720 cm^{-1}) and n.m.r. spectra. When the tetrahydroquinoline

(337e) was acetylated, it yielded a diacetylated product identified as

(394). It analyzed correctly for $C_{28}H_{25}N_3O_4$ and its i.r. spectrum

showed three C=O absorption bands at 1766 (ester), 1700 (lactam) and

1670 (cyclic amide). The n.m.r. spectrum of this compound had

three methyl signals at δ0.78, 1.86 and 2.18. The first of these

signals was surprisingly far upfield, a position not expected for any of

(393)

(394)

(395)

(396)
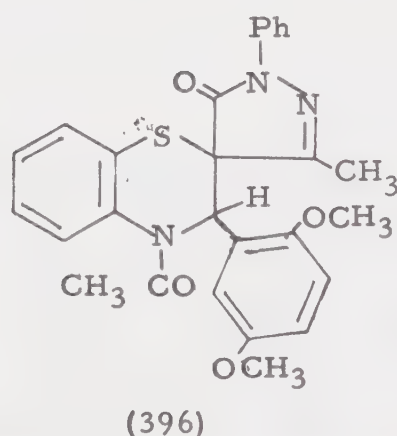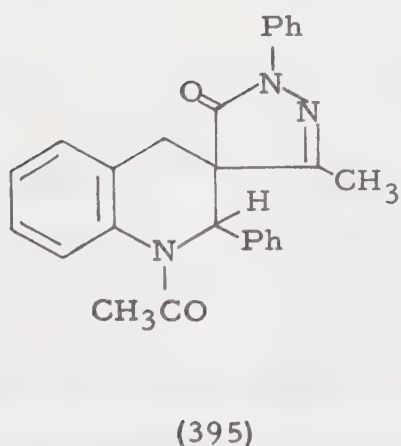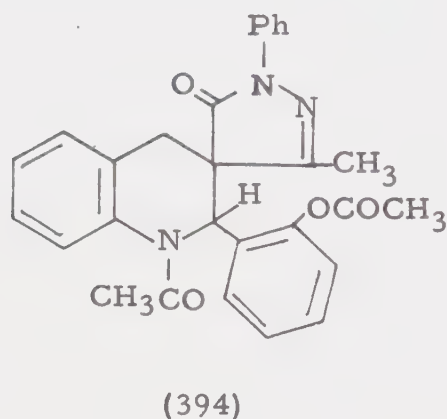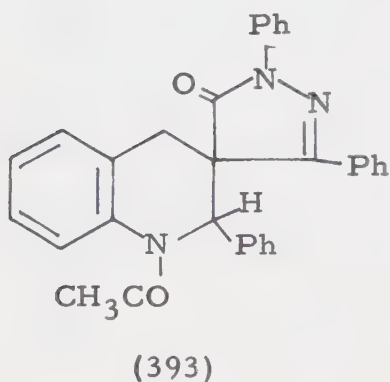
the methyl groups in compound (394). In order to assist in deciding

its origin, the acetyl derivatives (395) and (396) were prepared. The

results are summarized in Table 3 and indicate that it is the methyl

Table 3: The n.m.r. chemical shifts (relative to TMS) of the methyl and C_2—H signals in some acetyl derivatives of spiro-tetrahydroquinolines and spiro-dihydrobenzothiazines.

Compound	δ			
	$NCOCH_3$	$OCOCH_3$	$N{=}\overset{\mid}{C}{-}CH_3$	C_2—H
393	2.25	-	-	6.5
394	2.18	1.86	0.78	6.25
395	2.20	-	0.88	6.13
396	2.22	-	1.00	*
391	2.23	2.1	-	*
392	2.24	1.93	-	*
397	2.23	-	1.74	5.16
337b[†]	-	-	1.88	

* located within aromatic multiplet.

[†] is presented here for comparison

group on the pyrazolone ring which produces the upfield methyl signal in compound (394). A tentative explanation, based on the examination of Dreiding models, is that the $N=\overset{\mid}{C}-CH_3$ group is forced to align itself on top of the phenyl ring at C-2 of the tetrahydroquinoline ring or C-3 of the dihydrobenzothiazine ring and thus is greatly shielded. In addition, the hydrogen atom attached to the same carbon atom as the phenyl ring is forced into the plane of this phenyl ring, adopting "aromatic-like" character and therefore a downfield position. This explanation is supported by a study of the spectrum of the acetyl derivative (397) which lacks an aromatic substituent at C-2 of the tetra-hydroquinoline ring. In the n.m.r. spectrum of this compound, the pyrazolone methyl signal came to resonance at $\delta 1.74$. This signal was found to be at $\delta 1.88$ in the non-acetylated tetrahydroquinoline (337b, i.e., 397, H for $COCH_3$).

(397)
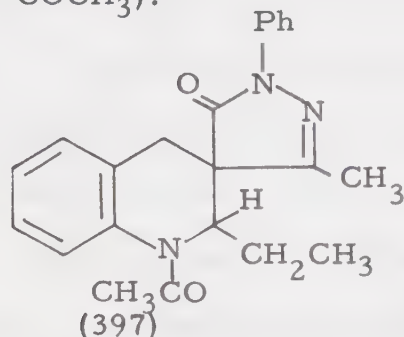
(b) <u>Reductions:</u> Whereas sodium borohydride reduction of the imine (385) in aqueous dioxane gave no crystalline products, similar reduc-tions of the isomeric spiro-tetrahydroquinolines (337a, b, c and e) yielded amphoteric products which analyzed for $C_{18}H_{18}N_3OR$. The ease of solubility of these products in aqueous sodium hydroxide suggested the presence of an enolizable hydrogen at C-4 of the pyrazo-lone nucleus. Structure (398) is suggested for the reduction products; this suggestion is supported by the spectral characteristics of these

(398 NH) ⇌ (398 OH)
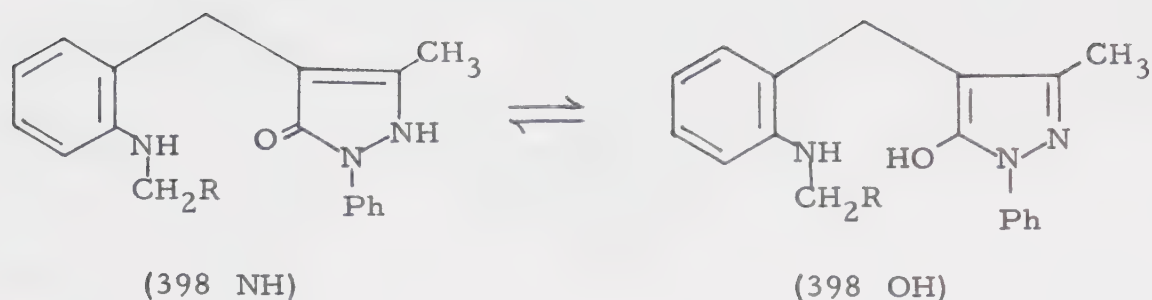
a, R=CH$_3$

b, R=C$_2$H$_5$

c, R=Ph

d, R=o-hydroxyphenyl

products. Their i.r. spectra displayed an N−H absorption band around 3300 cm^{-1}, lacked C=O absorption and showed broad absorption between 2100 and 3300 cm^{-1} which could be attributed to a bonded OH stretching band. The n.m.r. spectra of these products were very informative. In addition to the pyrazolone methyl signal and the aromatic signal, two deuterium-exchangeable protons and two methylene signals were also present. One methylene signal was a singlet while the other was a singlet or multiplet depending on the adjacent substituent (R). The mass spectra (Fig. 9) of the amphoteric products also supported the suggested structures (398). Some of the fragment ions in these spectra are tentatively identified in Scheme 21. The presence of ions a and b are of special interest since both contained an intact NHCH$_2$R unit. Unlike compounds (398a) and (398b) which expelled the substituent (R) as a radical and gave fragment c, compound (398c, R=Ph) lacked this ion, but instead expelled a C$_7$H$_7$ radical to give an ion of medium intensity at m/e 278.

Reductions of the spiro-tetrahydroquinolines (337a, b
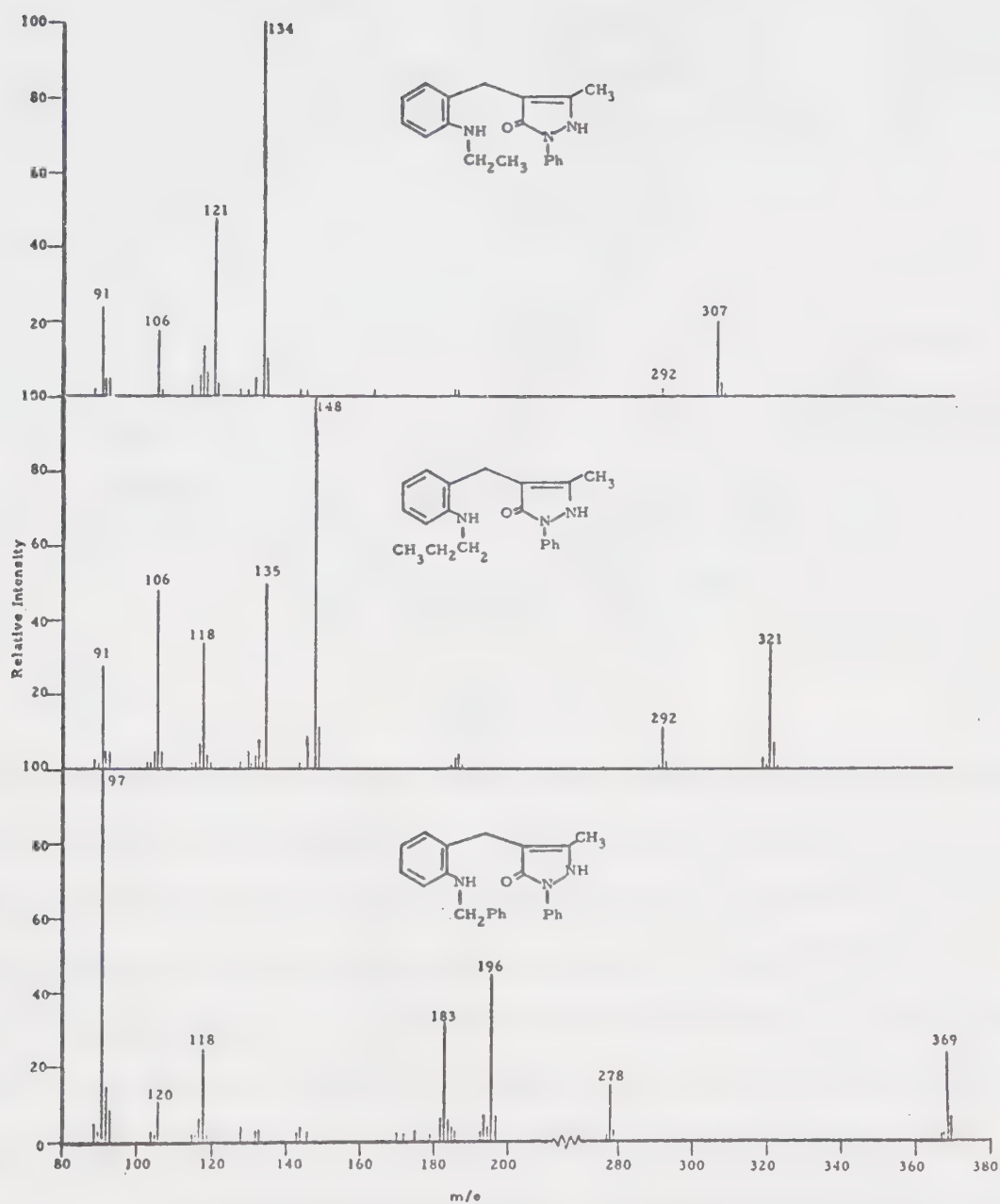
Fig. 9: Portions of the mass spectra of 4-(2-substituted aminobenzyl)-3-methyl-1-phenyl-3-pyrazolin-5-ones (398a, b, c).
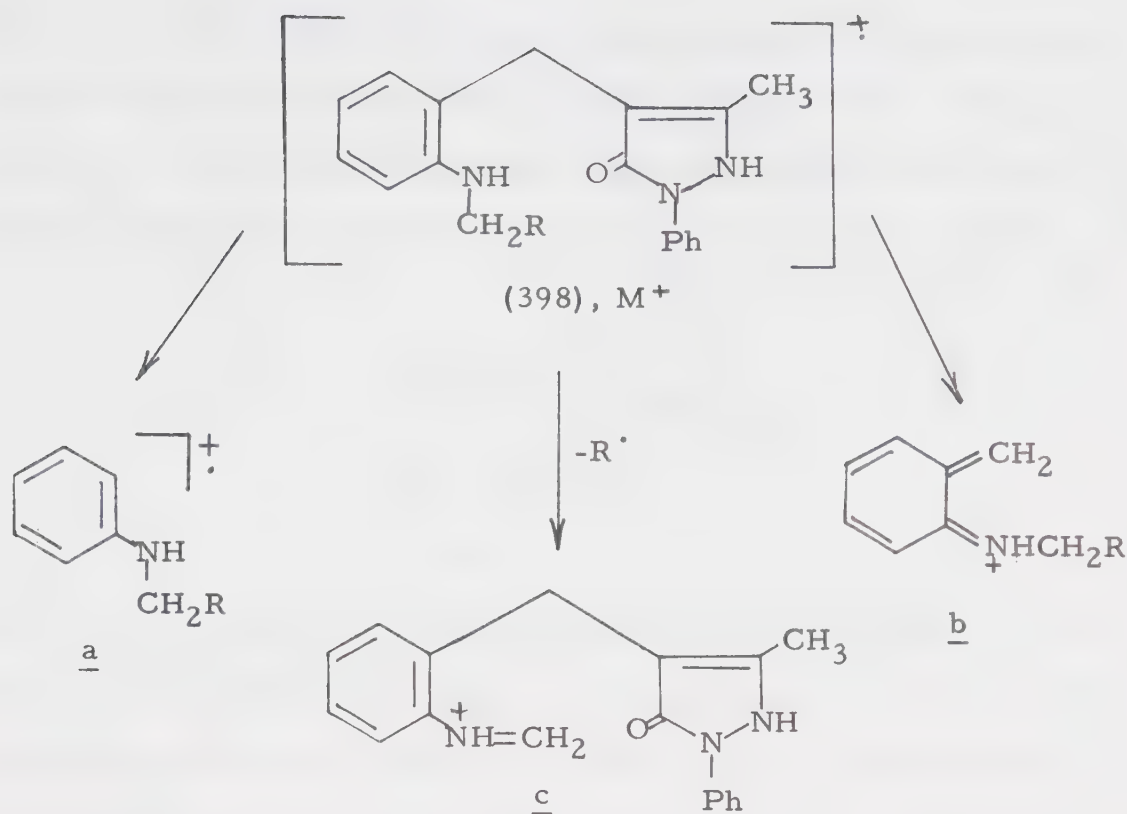
Scheme 21

and c) were also performed using lithium aluminum hydride in ether.
Two products were isolated from each reduction mixture, the minor
product was basic while the major product was amphoteric. The
proportion of these compounds was virtually reversed when the
reduction of (337a) was carried out in tetrahydrofuran. In contrast,
only the amphoteric product was obtained, when (337c) was reduced
with lithium aluminum hydride/aluminum chloride in ether.

The amphoteric products were identical to the compounds
obtained by sodium borohydride reduction of 337a, b and c, i.e. 398a,
b and c respectively. The basic products analyzed for $C_{18}H_{18}N_3R$
(R=CH_3, C_2H_5 or Ph) and their mass spectra displayed molecular ions
at appropriate m/e values for these formulae. This indicated that
the lactam C=O groups were reduced by the action of lithium aluminum
hydride, a reagent which is known to reduce pyrazolones to pyrazoline

and pyrazolidine derivatives (Bowman and Franklin, 1957; Hinman
et al, 1960; Bouchet et al, 1966; Elguero et al, 1971). The basic
properties, the elemental analyses and the mass spectra of these
products suggested that they were pyrazoline derivatives (399).
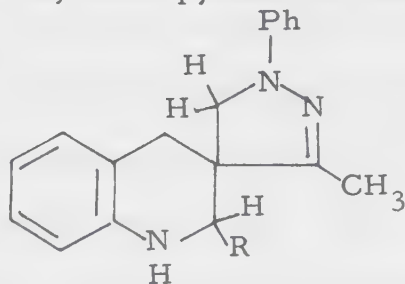
(399)

Their i.r. spectra lacked carbonyl absorptions. However, each had
two absorption bands near 3400 cm^{-1} (sharp) and 3300 cm^{-1} (broad)
which was somewhat puzzling since only one N—H stretching band
was expected.

Part II: REDUCTIONS OF 4-(2-NITROPHENYLTHIO)-2-

PYRAZOLIN-5-ONES.

Introduction:

A related investigation to the one discussed in part I is
the study of the sodium borohydride/palladium-charcoal reduction of
some 4-(2-nitrophenylthio)pyrazolin-5-ones to see whether cyclic
N-hydroxy compounds could be obtained.   The reduction of four of
these derivatives (400 and 401) was initially performed by Pound
(1970).   Two products were obtained from the sodium borohydride/
palladium-charcoal reduction of 3-methyl-4-(2-nitrophenylthio)-1-
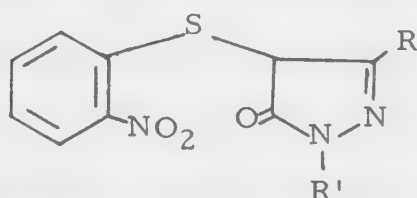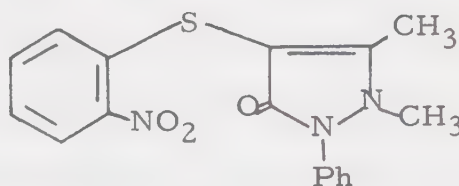
(400)   (401)

a, R = CH$_3$, R' = Ph

b, R = R' = Ph

c, R = CH$_3$, R' = H

phenyl-2-pyrazolin-5-one (400a).   These were identified as 9,9a-
dihydro-9-hydroxy-3-methyl-1-phenyl-1H-pyrazolo[4,3-b]-1,4-
benzothiazine (402) and spiro [benzothiazoline-2,4'-(3'-methyl-1'-
phenyl-1H-pyrazolin-5'-one)] (403).   The N-hydroxy compound (402)
was reported to be readily oxidized in air to the spiro benzothiazoline
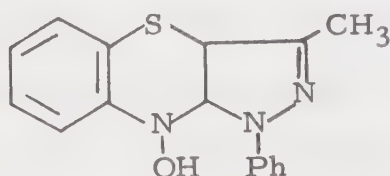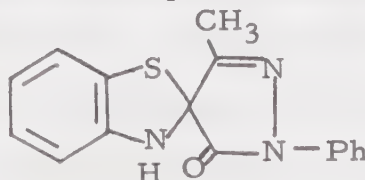
(402)   (403)

derivative (403) and a mechanism for this transformation was

suggested.   Although the structure of the spirobenzothiazoline (403)

is not in question, the structure of the proposed N-hydroxy compound

(402) became doubtful for two reasons:

(a) The compound prepared by Pound (1970) was found to be amphoteric.

An investigation of the properties of some cyclic N-hydroxy compounds

described earlier in this thesis suggested that the N-hydroxy function

in such a structure (402) would be neutral and therefore such a

compound should be insoluble in alkali.

(b) The ease of conversion of the proposed N-hydroxy compound (402)

to the spiro-benzothiazoline (403) suggested structural similarities,

otherwise, a rather exotic rearrangement mechanism is required to

explain this facile conversion.

For these two reasons, the reduction of two 4-(2-nitro-

phenylthio)-2-pyrazolin-5-ones was reinvestigated.   These two

compounds were 3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-

5-one (400a) and 4-(2-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one

(400b).

Preparation of two 4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-ones

(400a,b).

Both compounds (400a) and 400b) were prepared by one of

the methods reported by Coutts et al (1966).   The condensation of

o-nitrobenzenesulfenyl chloride (404) with 3-methyl-1-phenyl-2-

pyrazolin-5-one (405a) in acetonitrile resulted in a good yield of

3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a).

Similarly, 4-(2-nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one

(400b) was obtained by the reaction of o-nitrobenzenesulfenyl chloride

(404) with 1,3-diphenyl-2-pyrazolin-5-one (405b).

(404) + (405) → (400) [CH form] ⇅ (400) [OH form]

a, R=CH₃

b, R=Ph
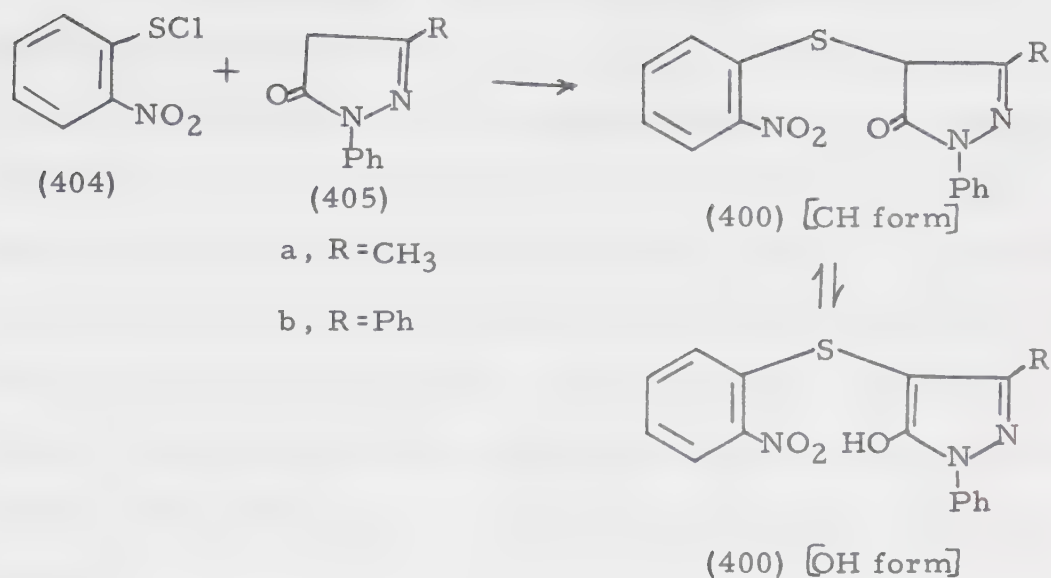
Reductions of 3-methyl-4(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a).

Method (A): Use of sodium borohydride and palladium-charcoal in sodium hydroxide solution.

Because of its ability to enolize, this pyrazolone derivative is soluble in dilute alkalis. Accordingly, the sodium borohydride/palladium-charcoal reduction was carried out initially in 10% sodium hydroxide solution. On completion of the reaction, the filtrate was acidified with dilute acetic acid to yield a copious cream coloured product (E) which was readily soluble in 95% ethanol. On standing, however, a product precipitated from the solution. This compound, product (F), was no longer soluble in ethanol or most other organic solvents. Concentration of the mother liquor remaining after removal of product (F) led to the separation of variable yields of the previously identified spiro[(benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (403).

The elemental analyses of both products (E) and (F) indicated isomeric structures, $C_{16}H_{15}N_3OS$. The mass spectra of both were virtually identical and confirmed their molecular weights (297). The i.r. and n.m.r. spectra of both products were also identical. The ethanol-insoluble product (F) could be reconverted to product (E) by dissolving (F) in dilute sodium hydroxide solution and acidifying with dilute acetic acid. Because of this ease of interconversion, it was concluded that products (E) and (F) were diamorphic, although such a difference in solubility characteristics is difficult to explain.

In order to identify the structure of this amphoteric product, the number of acidic groups in (F) was determined titrimetrically. The equivalent weight of this compound was found to be 148 which indicated that (F) possessed two acidic groups. The insolubility of this compound in sodium carbonate solution suggested that both the acidic groups were phenolic and/or enolic. At this point, it was possible to conclude that the proposed N-hydroxybenzothiazine structure (402) for product (F) was no longer valid.

Attempts were made to prepare chemical derivatives of (F) in order to help in positive identification. Although a pure acetylated derivative could not be prepared, it proved possible to isolate pure methyl and benzoyl derivatives. Methylation by means of dimethylsulfate in dilute sodium hydroxide solution produced a dimethyl derivative of (F) of molecular weight 325 (mass spectrum). Its i.r. spectrum showed a C=O absorption band at 1670 cm^{-1} in addition to an N—H stretching band at 3345 cm^{-1}. This indicated that product (F) also possessed a C=O group. The presence of an

enolizable hydrogen at C-4 of the pyrazolone ring accounts for the
apparent absence of C=O absorption in the i.r. spectrum of (F)
[which, however, did have a medium intensity absorption band at
1626 cm.$^{-1}$ (bonded C=O?)] and also for its solubility in dilute
alkali.   The dimethyl derivative was no longer soluble in sodium
hydroxide solution due to the absence of this enolizable hydrogen.

Benzoylation of product (F) was achieved by treating a
cold sodium hydroxide solution of this product with benzoyl chloride.
The elemental analysis ($C_{37}H_{27}N_3O_4S$) and the mass spectrum (M^+,
m/e 609) of the resulting product revealed it was a tribenzoate.   An
accurate mass determination of the molecular ion was in agreement
with this molecular formula.

Product (F) was also found to be very readily oxidized to
compound (G) which Pound (1970) identified as the spiro(benzothiazo-
line)pyrazolone (403).   Thus, when (F) was suspended in ethanol and
the suspension exposed to the atmosphere, the compound first entered
solution.   On standing, however, yellow cyrstals identical with product
(G) precipitated.   The same occurred when (F) was dissolved in
DMSO-d$_6$ in order to record its n.m.r. spectrum; a mixture of both
compounds (F) and (G) was indicated by the spectrum.   Another
spectrum taken on the same sample after a few hours demonstrated
only the presence of compound (G).   This ease of oxidation of (F) to
(G) indicated a similarity in both structures.

Based on all these findings, the structure of product (F)
is concluded to be 4-(2-mercaptophenylamino)-3-methyl-1-phenyl-2-
pyrazolin-5-one (406).   The absence of lactam C=O absorption in
the i.r. spectrum of (406) suggests that the compound exists in the

(406)   [CH form] ⇌ (406)   [OH form]

(406)   Ph   [NH form]
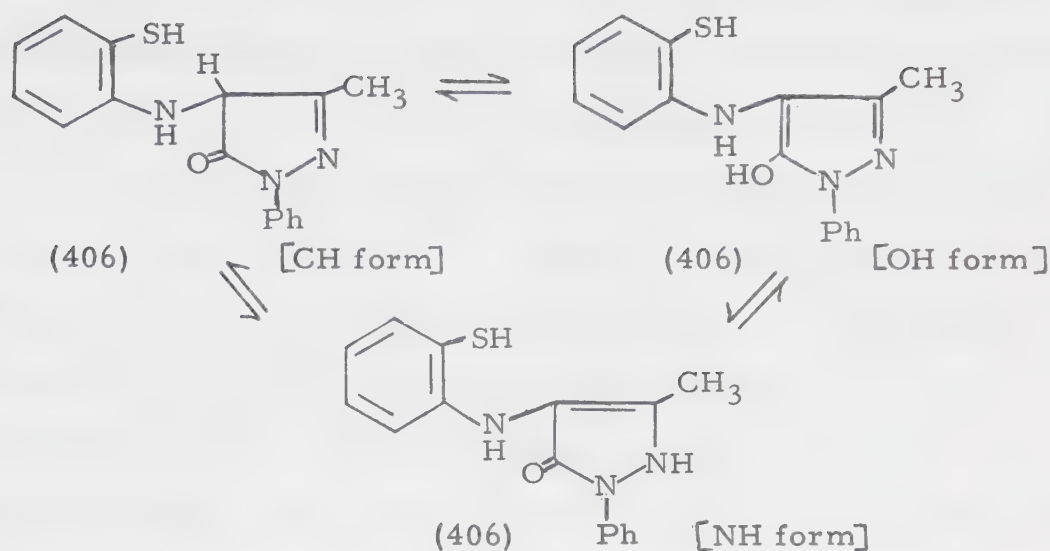
enolic form in the solid state. However, a closer look at the spectrum

revealed the presence of a medium intensity absorption at 1626 cm^{-1}.

This band could be due to a strongly bonded $C=O$ absorption of the

"NH" tautomer which is normally expected to be around 1670 cm^{-1}

(Newman and Pauwels, 1969). The absence of a similar band in the

i.r. spectrum of the diacetyl, dimethyl and tribenzoyl derivatives of

(414) indicated that this assignment might be correct. Lack of

solubility of compound (406) in most organic solvents and its ease of

conversion to the spiro-benzothiazoline (403) hindered measuring the

i.r. spectrum in solution. The absence of any $C=O$ absorption

close to 1700 cm^{-1} indicated the absence of any contribution from

the "CH" form. The presence of a broad absorption band between

2400 and 3300 cm^{-1} masked the S—H stretching absorption which

normally occurs as a sharp, easily recongnized band in the range

2550-2600 cm^{-1}, however, the weak maximum at 2600 cm^{-1} could

be due to this absorption. The apparent lack of a stretching band for

the thiol group earlier (Pound, 1970) led to the incorrect assignment

of structure (402) to product (F). That the thiol function was present

in (407) was clearly demonstrated in the mass spectrum (Fig.10) of this compound and was inferred from the i.r. and mass spectra of the diacetyl, dimethyl and tribenzoyl derivatives (see later).

The n.m.r. spectrum of compound (406) was measured immediately after dissolving it in DMSO-d_6, that is before oxidation could occur. It showed a three-proton signal at δ 2.05 which was attributed to the methyl group of the pyrazolone ring. The only other feature in the spectrum was the presence of a twelve proton multiplet between δ 6.3 and 8.0; two (or three) of these protons were exchangeable with deuterium. The signals of both the N–H and S–H protons as well as that of the pyrazolone ring proton are probably masked under this aromatic multiplet. Due to the adjacent nitrogen and sulfur atoms, the pyrazolone ring proton might be expected to appear downfield within the aromatic region. This suggestion is supported by the fact that no separate signals for the pyrazolone proton are detected in the n.m.r. spectra of the 4-(2-nitrophenylthio)-2-pyrazolin-5-one derivatives (400).

Elemental analysis, i.r. and n.m.r. data, therefore, are in agreement with the suggested structure (406) for the amphoteric product (F). This structure can also explain the ease of oxidation of product (F) to product (G) which was demonstrated on several occasions.
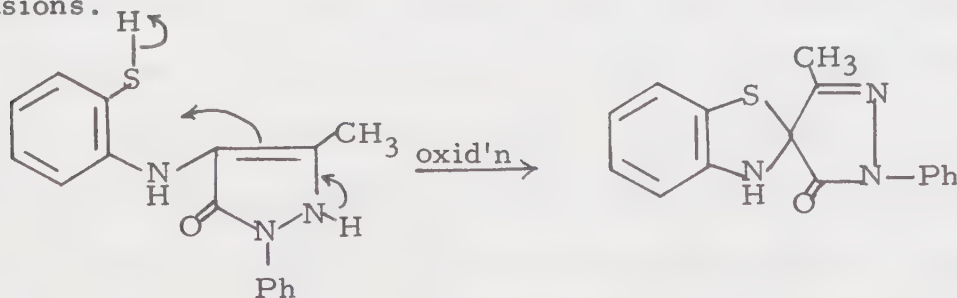
Product F (406)   Product G (403)

The mass spectrum of 3-methyl-4-(2-mercaptophenyl-amino)-1-phenyl-2-pyrazolin-5-one (406) is shown in Fig. 10 and its suggested fragmentation pathways are outlined in Scheme 22. The
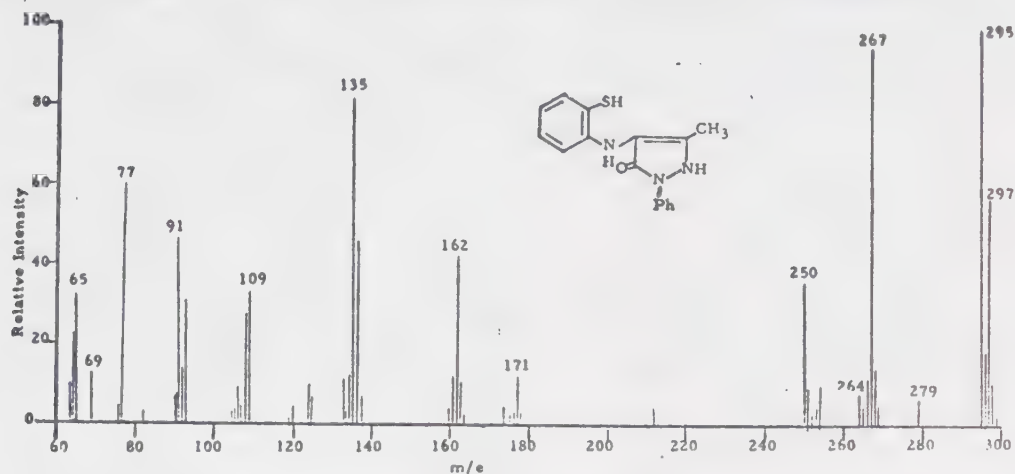
Fig. 10: A portion of the mass spectrum of 4-(2-mercaptophenyl-amino)-3-methyl-1-phenyl-3-pyrazolin-5-ones (398a, b, c).

major fragment (a) resulted from expulsion of a hydrogen molecule to give the spiro-benzothiazoline (403) and then followed the same fragmentation pattern of this compound; these will be discussed later in this thesis (part III A). Pound (1970) found that increasing the temperature of the probe or the length of time of bombardment resulted in increasing the intensity of the peak at m/e 295 which is the molecular ion of the spiro-benzothiazoline (403). It was suggested that rapid oxidation of compound (406) occurred in the probe of the spectrometer. Minor fragmentation pathways of compound (406) were very informative. These were the loss of an SH radical and a water molecule from the molecular ion; the first fragmentation was support-ed by the presence of a metastable ion. None of these fragments were found to be present in the mass spectrum of the spiro-benzo-thiazoline (403). Attempts to deuterate the amphoteric compound (406) were unsuccessful and resulted only in the formation of the

deuterated spiro-benzothiazoline derivative (M^+, m/e 296).
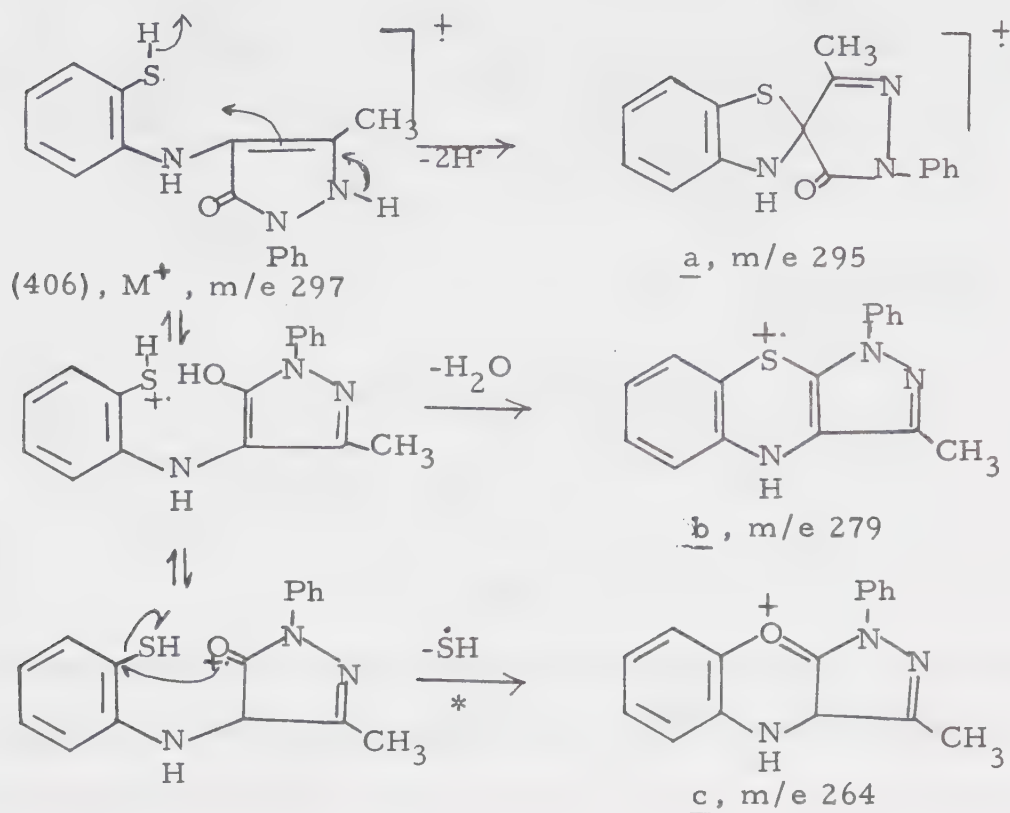
Scheme 22

A mechanism for the formation of the 4-(2-mercapto-phenylamino)pyrazolone derivative (406) from the nitrophenylthio-pyrazolone (400a) is suggested in Scheme 23. This is reminiscent of the work reviewed by Loudon and Tennant (1964) who considered that the nitro group can provide an electrophilic centre for additive reactions of the type exemplified by an aldol condensation:

$$\bar{O}-\overset{\overset{\displaystyle |}{+}}{N}=O \quad + \quad H_2CXY \quad \rightleftharpoons \quad \tilde{O}-\overset{\overset{\displaystyle |}{+}}{\underset{\underset{\displaystyle OH}{|}}{N}}-CHXY \qquad (5)$$

A similar intramolecular reaction can occur in the nitro compound (400a) between the active hydrogen at C-4 of the pyrazolone ring and the nitro group and this could lead to the heterocyclic intermediate (407). Reduction of (407) would result in the formation of the
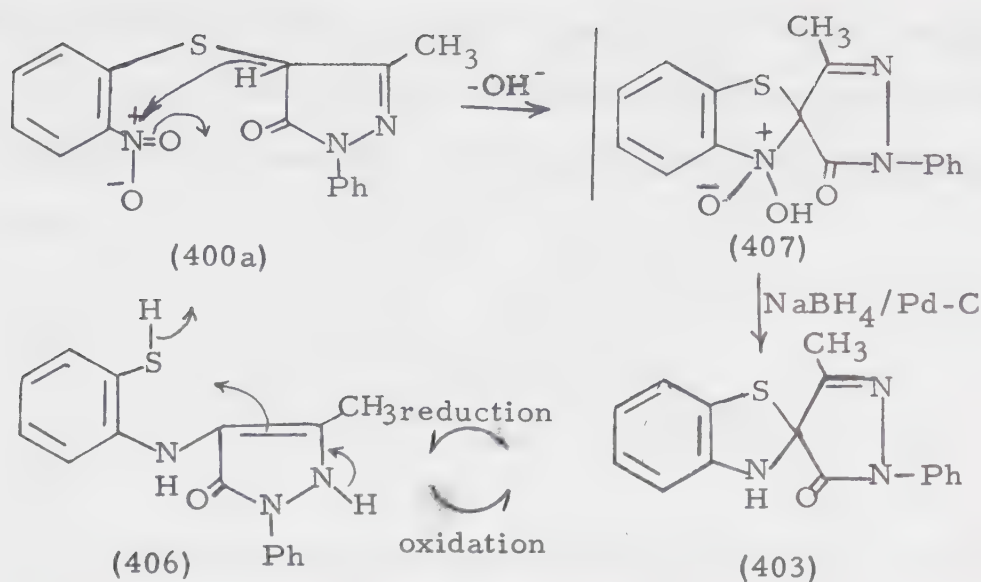
Scheme 23

spiro-benzothiazoline (403) which then further reduced to the 4-(2-mercaptophenylamino)pyrazolone (406). It is believed that this intramolecular condensation could also occur under neutral conditions because the same products were isolated when the nitro compound (400a) was reduced by zinc and ammonium chloride in aqueous ethanol.

In order to verify the assumption that the spiro-benzothiazoline(403) is obtained first then further reduced to compound (406), a pure sample of (403) was reduced by sodium borohydride and palladium-charcoal in a mixture of dioxane and dilute sodium hydroxide solution. As expected, compound (406) was the main product isolated.

Methylation of 3-methyl-4-(2-mercaptophenylamino)-1-phenyl-2-pyrazolin-5-one (406):

Initially, attempts to methylate this compound with diazomethane only resulted in its oxidation to the spiro-benzothiazoline (403). However, when (406) was dissolved in cold dilute sodium hydroxide solution and dimethyl sulfate was added dropwise, an insoluble product separated. Crystallization of this product yielded

a compound which analyzed correctly for $C_{18}H_{19}N_3OS$. An accurate

mass measurement of the molecular ion at m/e 325 verified this

formula. This compound was identified as the dimethyl derivative

2,3-dimethyl-4-(2-methylthiophenylamino)-1-phenyl-3-pyrazolin-5-

one (408).
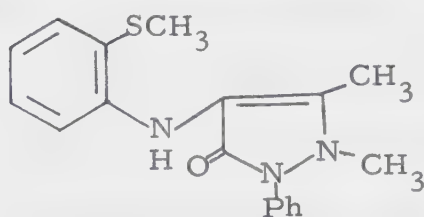
(408)

Methylation at N-2 of the pyrazolone nucleus was indicated

by the i.r. spectrum which displayed a C=O absorption band at 1670

cm^{-1}. Such a band is only expected when the pyrazolone ring exists in

the "NH" form (408) (Nakanishi, 1962; Newman and Pauwels, 1969).

The mass spectrum of this dimethyl derivative (Fig. 11, Scheme 24)
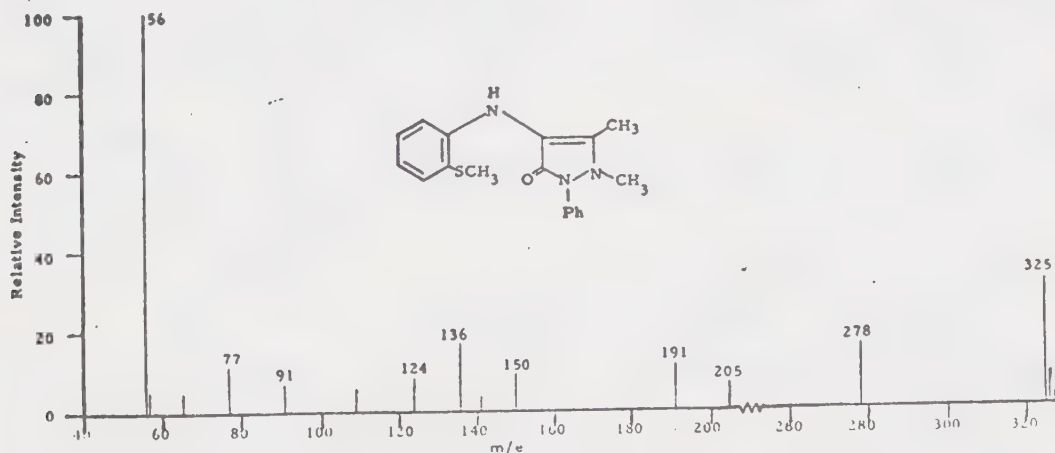
Fig. 11: A portion of the mass spectrum of 2,3-dimethyl-4-(2-
methylthiophenylamino)-1-phenyl-2-pyrazolin-5-one (408).

had a strong ion (the base peak) at m/e 56. This ion, which corres-

ponds to $CH_3-C\overset{+}{\equiv}N-CH_3 \longleftrightarrow CH_3-\overset{+}{C}=N-CH_3$, was found in the

spectra of antipyrine, aminopyrine (see part III A) and in the spectrum

of the N-methylpyrazolone (324) prepared earlier in this study. The

fact that S-methylation had occurred was substantiated by the chemical

properties and the mass spectrum of this compound. The product

obtained was no longer soluble in sodium hydroxide solution which

indicated replacement of the hydrogen of the thiol function. Also an

S—H stretching band was not detected in the i.r. or in the n.m.r.

spectra. The mass spectrum of this compound (Scheme 24) was most

informative. It gave a molecular ion at m/e 325 ($C_{18}H_{19}N_3OS$) and

an abundant $(M-47)^+$ fragment ion ($C_{17}H_{16}N_3O$). This accounted for

the loss of an SCH_3 radical from the molecular ion, a fragmentation

supported by the presence of a metastable ion. The loss of OCH_3 or

SCH_3 radicals from ethers or thioethers is not a common fragmenta-

tion pathway, but might be expected to occur if it leads to a stable

even electron cyclic ion such as (409). A similar ortho effect was
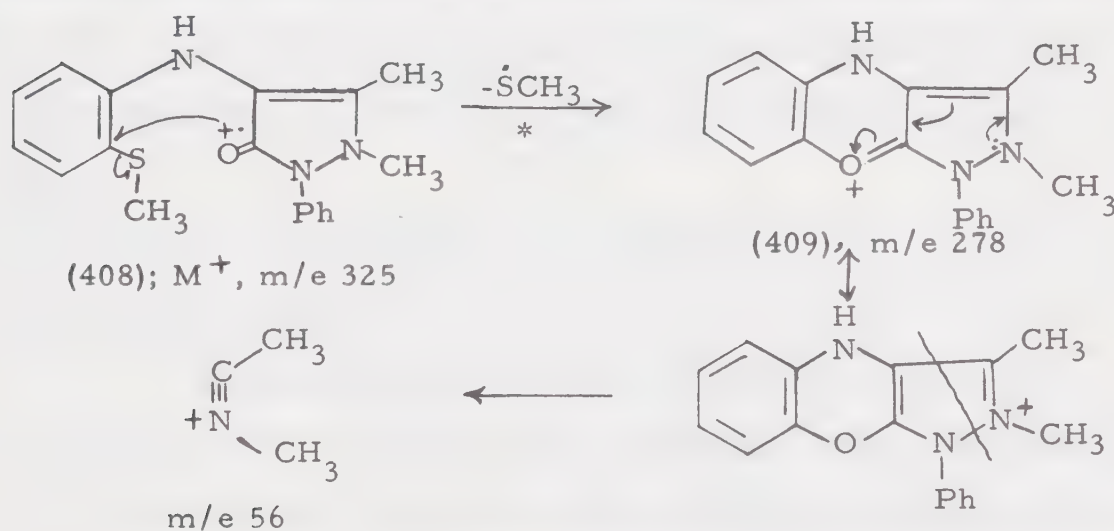
Scheme 24

recently reported by Cable et al (1972) who examined the mass spectra

of phenylhydrazones and 2,4-dinitrophenylhydrazones of ortho substi-

tuted benzaldehydes and acetophenones. They found that a fragment

ion resulted from the loss of the ortho group (I, Br, Cl, OH and OCH_3)

as a radical. This process leading to an $(M-X)^+$ ion was visualized

as the internal displacement of the ortho-substituent by the charge

localized on the amino nitrogen of the diphenylhydrazone (410) leading

to the even electron cyclic ion (411).

(410)   (411)
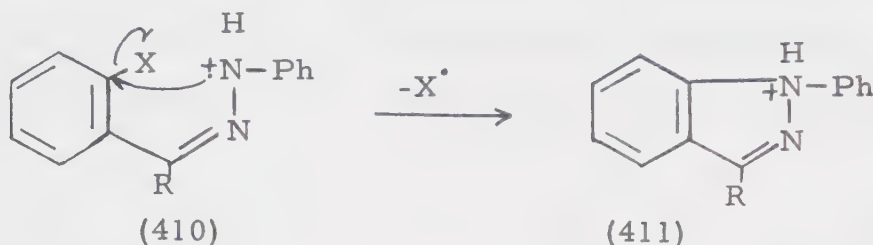
The n.m.r. spectrum of the methylated product was also

consistent with the proposed structure (408).   It displayed three

3-proton singlets at δ2.14, 2.39 and 3.03, which are assigned to the

C-CH_3, S-CH_3 and N-CH_3 groups respectively since the equivalent

C-CH_3 group in the non-methylated compound (406) was detected at

δ2.04 and the equivalent N-CH_3 group in antipyrene (329) came to

resonance at δ2.94.   The n.m.r. spectrum also contained a deuter-

ium-exchangeable proton at δ6.12 which was assigned to the N-H

proton.

Benzoylation of 3-methyl-4-(2-mercaptophenylamino)-1-phenyl-2-
pyrazolin-5-one (406):

Benzoylation of compound (406) was carried out in the

manner described by Pound (1970).   Treating a sodium hydroxide

solution of (406) with benzoyl chloride resulted in a semisolid which,

when chromatographed on a silica gel column,   produced several

dark oils.   One of these oils solidified on repeated trituration with

petroleum ether.   The elemental analysis ($C_{37}H_{27}N_3O_4S$) and the

mass spectrum (M^+ , m/e 609) of this compound revealed that it was

a tribenzoate derivative.   An accurate mass measurement of the

molecular ion was in agreement with this molecular formula.   Two

structures (412) and (413) were suggested earlier (Pound, 1970) for

this compound but these suggestions were based on identification of

the non-benzoylated derivative as the N-hydroxybenzothiazine (402).

However, after reassessment of this structure, the tribenzoyl

derivative is now identified as: 4-[N-benzoyl-N-(2-benzoylthio-

(412)   R=COPh   (413)
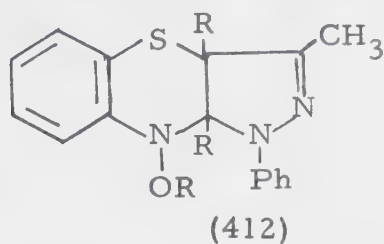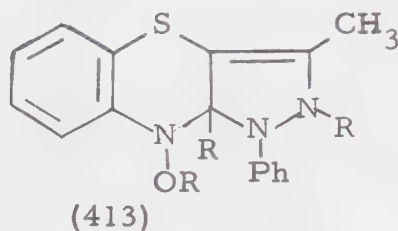
phenyl)amino]-5-benzoyloxy-3-methyl-1-phenylpyrazole (414).   That

O-benzoylation had occurred was shown from the i.r. spectrum which

(414)
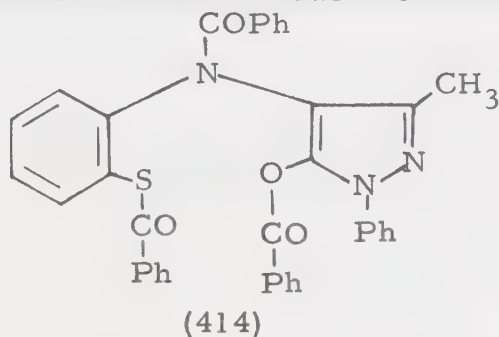
displayed a C=O absorption band at 1758 cm^{-1} (cf. p. 90) and by

examining the mass spectrum of the product which showed the

expulsion of a benzoyloxy radical (PhCOO$^{\cdot}$) from the molecular ion.

A strong metastable at m/e 391.04 indicated that this expulsion was,

at least in part, directly from the molecular ion.   Benzoylation of

both the NH and SH functions was apparent from the absence of any

NH or SH absorption bands in the i.r. spectrum.   In addition, a

C=O absorption band at 1679 could be attributed to both S-benzoyl

and N-benzoyl functions.   The latter is known to absorb in this region.

Also diarylthiol esters are reported to absorb close to 1685 cm^{-1}

(Nyquist and Potts, 1959; Baker and Harris, 1960; Bellamy, 1968).

The mass spectrum of compound (414) is shown in Fig. 12

and the proposed fragmentation pathway are presented in Scheme 25.
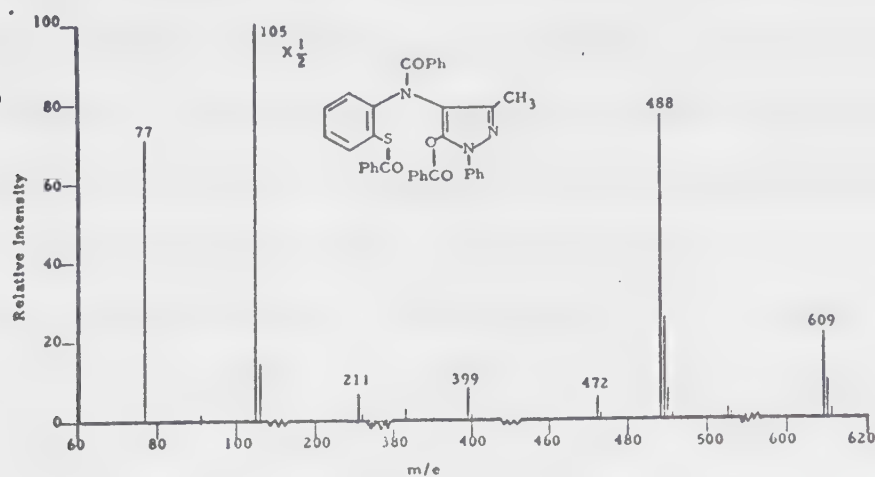
Fig. 12: A portion of the mass spectrum of 4-[(N-benzoyl-N-
(benzoylthiophenyl)amino]-5-benzoyloxy-3-methyl-1-
phenylpyrazole (414).
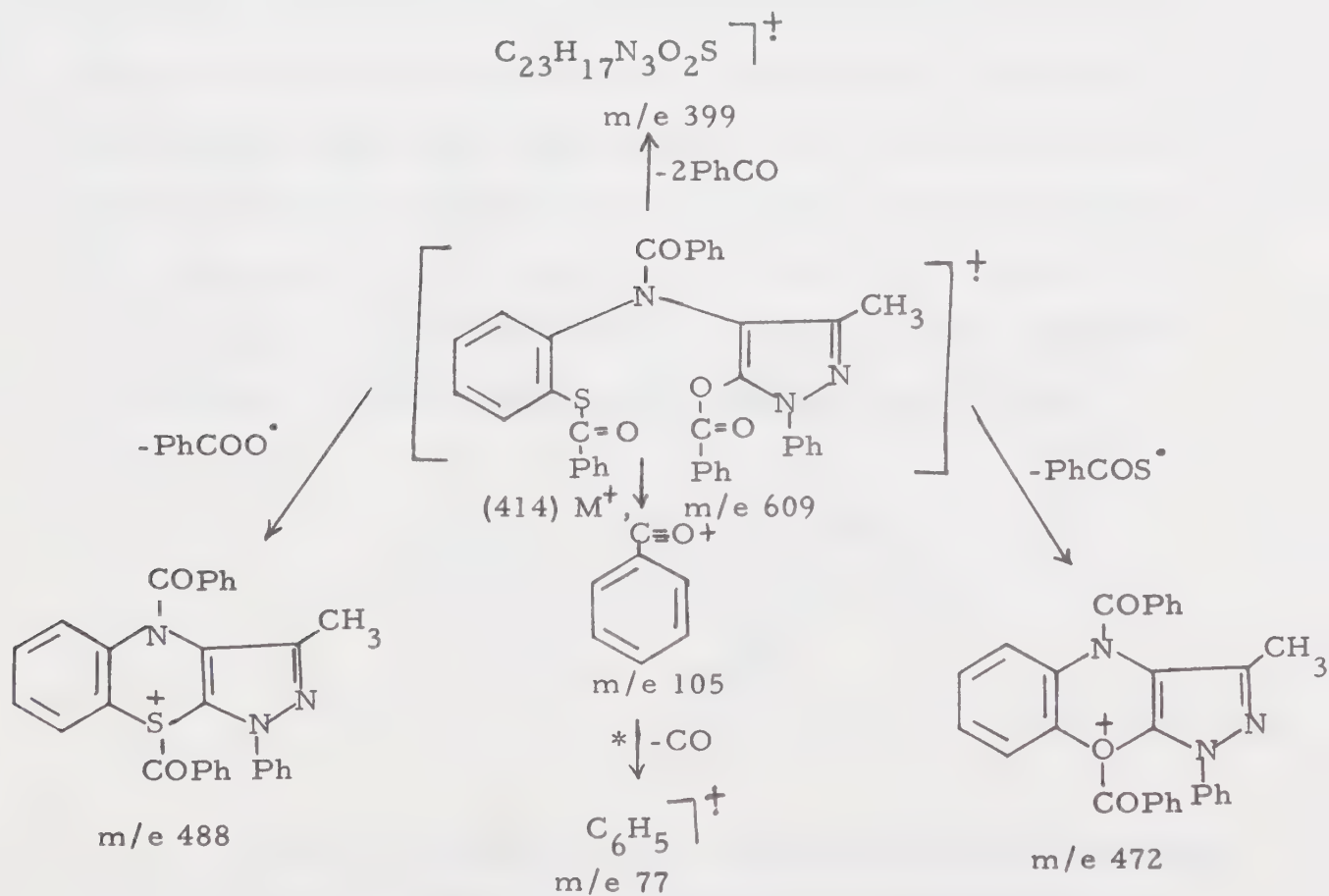
Scheme 25

In addition to the major loss of PhCOO° radical from the molecular

ions, two weak fragment ions at m/e 472 and m/e 399 correspond to

the expulsion of a PhCOS° and two PhCO° radicals from the molecular

ion. Although no metastables to support these two losses are present,

the absence of other ions in the spectrum suggested that they originate

directly from the molecular ion. As usual in all the benzoyl deriva-

tives, the spectrum showed a strong ion at m/e 105 (PhCO)$^+$ which

expelled a carbon monoxide molecule to give another strong ion at

m/e 77 (C_6H_5).

Acetylation of 3-methyl-4-(2-mercaptophenylamino)-1-phenyl-2-pyrazolin-5-one (406)

Trials to acetylate compound (406) by heating with acetic

anhydride or acetyl chloride in benzene were unsuccessful and resulted

only in the isolation of the spiro-benzothiazoline (403). However,

when compound (406) was treated with acetic ahydride in cold pyridine,

a yellow NaOH-insoluble product was collected. Crystallization of

this compound proved difficult but the i.r., the n.m.r. as well as

the mass spectra indicated that it was a diacetate which is identified

as 5-acetyloxy-3-methyl-4-(2-acetylthiophenylamino)-1-phenyl-

pyrazole (415).
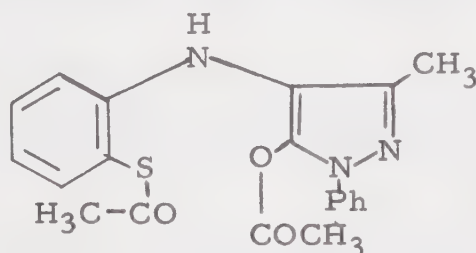
(415)

The i.r. spectrum of this compound had an N—H absorption

at 3368 cm^{-1} and two C=O absorption bands at 1720 (SCOCH$_3$) and

1788 (OCOCH$_3$) cm^{-1}.   Alkyl and aryl thioesters of the type

C$_6$H$_5$ SCOR are known to absorb near 1710 cm^{-1} (Bellamy, 1968).

The presence of the thioester C$=$O absorption in compound (415) at

a slightly higher frequency than reported may be due to the presence

of a bulky substituent in the o-position (cf. Schubert and Sweeney,

1955).

The n.m.r. spectrum of (415) contained three methyl

signals at δ2.15, 2.22 and 2.44 and one D-exchangeable proton at

δ6.2 (N—H).   A molecular ion at m/e 381 in the mass spectrum of

the product is in agreement with the diacetate structure.   This ion

fragmented by two successive losses of ketene molecules.   Also, a

loss of a molecule of acetic acid from both the molecular ion and

the (M-42)$^{+}$ion was demonstrated by the fragment ions at m/e 321 and

279.

Attempts to isolate the diacetyl derivative (415) in a pure

crystalline form gave only, after long standing in ethanol, a crystal-

line compound which was shown to be the spiro-benzothiazoline (403).

This compound is believed to be formed from the diacetyl derivative

(415) by hydrolysis then oxidation since none of the spiro-benzothi-

azoline (403) was demonstrated in the i.r. or the n.m.r. spectra of

the crude acetylation product.

Method (B):   Use of sodium borohydride and palladium-charcoal in

dioxane.

It was shown earlier in this study that changing the solvent

system in the sodium borohydride/palladium-charcoal reductions of

the o-nitrobenzylidene derivatives (318) from sodium hydroxide

solution to dioxane resulted in the formation of cyclic N-hydroxy

compounds as major products. To find out whether it was possible to obtain any related N-hydroxy compounds from the o-nitrophenylthio derivative (400a), the sodium borohydride/palladium-charcoal reduction was carried out in dioxane. However, even when several modifications in the reduction time and/or the quantities of reducing agents were made, only two products, the thiol (406) and the spiro-benzothiazoline (403) were obtained, but this time the latter (403) was the major product. The amine (416) was not isolated in any appreciable amount from the reduction mixture; this amine was claimed earlier (Pound, 1970) to have been the major product obtained when the sodium borohydride/palladium-charcoal reduction of (400a) was carried out in dioxane.

Method (C):   Use of iron and ferrous ammonium sulfate.

Reduction by means of iron and ferrous ammonium sulfate is a common method for the reduction of nitro compounds to the corresponding amines (Hickenbottom, 1959). However, when this reduction was performed earlier in this thesis with the o-nitrobenzyl derivative (319a), the cyclic N-hydroxy compound (338) was isolated along with the amine (321). When the o-nitrophenylthio compound (400) was reduced in a similar way, no cyclic N-hydroxy compounds were obtained; only the amine (416) was isolated in a good yield. Identification of this amine was based on comparison of its physical and chemical properties with those reported earlier (Angelini and Martani, 1955; Pound, 1970). The i.r. spectrum of this amine (416) indicated that it is present in the solid state in the NH $\rightleftharpoons$ OH forms. As observed with the related amines (321), the C$=$O and the primary amines absorption bands of compound (416) were located at lower

frequencies than expected (1625, 3145 and 3295 cm^{-1}). This shift

(416) [NH form]

(416) [CH form]   (416) [OH form]
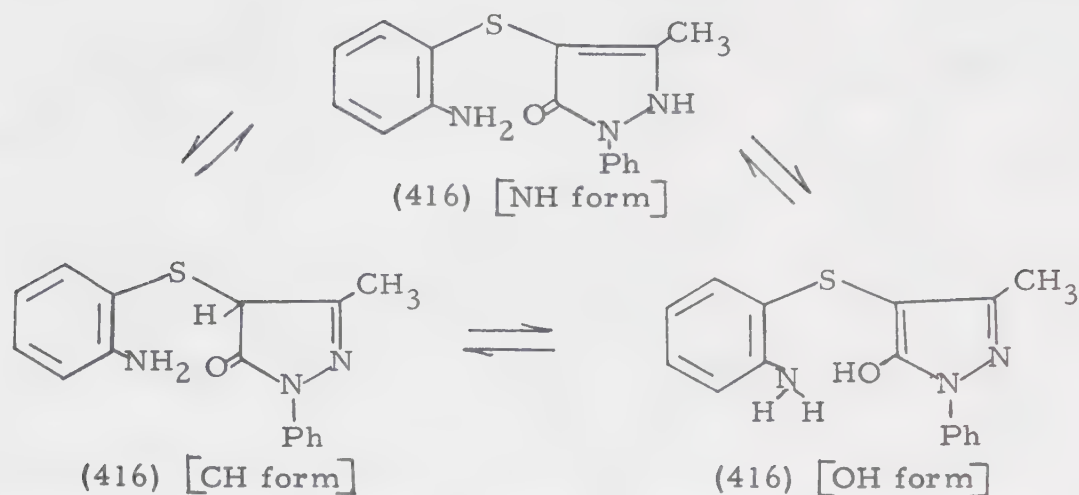
may be accounted for by the possibility of intermolecular or even

intramolecular hydrogen bonding.

The mass spectrum of compound (416) was recorded (Fig.

13) and its major fragmentation pathways are suggested in Scheme 26 .
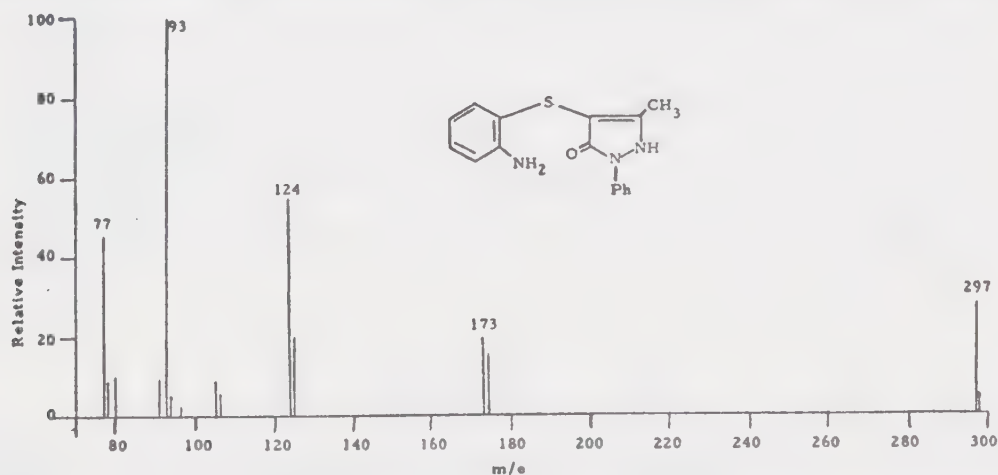
Fig. 13:   A portion of the mass spectrum of 4-(2-aminophenylthio)-
3-methyl-1-phenyl-3-pyrazolin-5-one (416).

Cleavage of the C—S bond occurred on both sides of the sulfur atom.

Some differences exist in the behavior, under electron impact, of

this amine (416) and the related amines (321) discussed earlier (p. 83).

These included the absence here of both the (M-18)$^+$ and (M-19)$^+$

ions.   This spectrum also had an ion at m/e 105 (PhN$_2$)$^+$ which was

absent from the spectrum of (321).

CH$_3$ ... -H· ...

HO ... N–N ... Ph

O ... N$^+$=N ... Ph ... CH$_3$ ... m/e 173

S· ... NH$_2$ ... ?

S ... NH

S ... CH$_3$ ... NH$_2$

(416) M$^+$, 297 (C$_{16}$H$_{15}$N$_3$OS)

S ... CH$_3$ ... O ... N ... Ph

H ... NH$_2$ ... m/e 93

HC· ... CH$_3$ ... O ... N–N ... Ph ... *

SH ... NH$_2$ ... m/e 125 ... -H·

S ... NH$_2^+$ ... m/e 124

Scheme 26

Method (D): Use of Zinc and ammonium chloride.

This method is commonly used to prepare hydroxylamine derivatives from nitro-compounds. Reduction of (400a) was carried out under nitrogen using aqueous ethanol as a solvent due to the insolubility of the nitro compound (400a) in water alone. This resulted in an excellent yield of the spiro-benzothiazoline (403). When the reduction period was prolonged, the thiol (406) was the main product. Replacing aqueous ethanol by aqueous tetrahydrofuran as a solvent

system also resulted in isolation of the same products. In no case, was it possible to isolate any hydroxylamine or cyclic N-hydroxy compounds.

Method (E): Catalytic Hydrogenation.

Finally, the nitro compound (400a) was reduced catalytically over platinum. Formation of cyclic N-hydroxy compounds was not likely using this strong reducing system; however, it was of interest to see if a similar reaction to that which occurred earlier during the catalytic hydrogenation of the nitrobenzyl derivatives (319a,b) would take place. This did not occur. Instead, a small amount of the thiol (406) was precipitated during the reduction and was separated from the platinum catalyst by its solubility in dilute alkali solution. The filtrate, after evaporation, yielded the spiro-benzothiazoline (403) as the major product. When the same reduction was repeated under pressure a third product identified as the amine (416) was also isolated from the reduction mixture.

Reductions of 1,3-diphenyl-4-(2-nitrophenylthio)-2-pyrazolin-5-one (400b):

Only three of the methods used previously with the methyl analog (400a) were tried on this nitro derivative (400b). These were the sodium borohydride/palladium-charcoal reduction in 10% sodium hydroxide solution, the reduction by zinc and ammonium chloride and the reduction by iron and ferrous ammonium sulfate. The first two methods produced pure crystalline products, none of which was a cyclic N-hydroxy compound. Trials to isolate pure cyrstalline products from the reaction mixture obtained by the third method were not successful.

Reduction by sodium borohydride/palladium-charcoal was carried out in 10% sodium hydroxide solution in the same way described earlier for reduction of (400a). Two compounds were isolated from the reduction mixture and were identified as 1,3-diphenyl-4-(2-mercaptophenylamino)-3-pyrazolin-5-one (417) and spiro-[benzothiazoline-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (418). The latter compound is believed to be formed by the oxidation of the thiol (417) during crystallization since the i.r. spectrum of the crude product was devoid of any $C=O$ absorption near 1700 cm^{-1}.
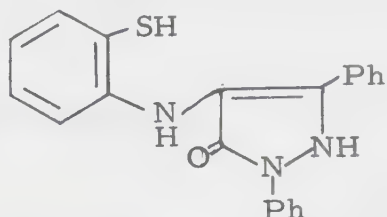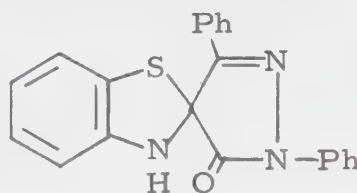
(417)   (418)

Compound (417) was earlier identified by Pound (1970) as the isomeric N-hydroxybenzothiazine (402, Ph instead of CH_3). However, the similarities in physical and chemical properties of this compound and the thiol (406) led to the conclusion that the proposed structure (417) is more likely. This compound which was soluble in dilute alkali solutions analyzed correctly for $C_{21}H_{17}N_3OS$. Its i.r. spectrum and mass spectrum (Fig. 14) (M‡, m/e 359) were similar to those of the methyl analog (406) and consistent with the proposed structure (417). The molecular ion fragmented mainly by the loss of a hydrogen molecule yielding the spiro-benzothazoline (418). Two minor but diagnostic fragment ions were also present and were due to the expulsion, from the molecular ion, of a molecule of water and an SH radical to give ions at m/e 341 and m/e 326 respectively. These ions are believed to be analogous to those proposed earlier for the
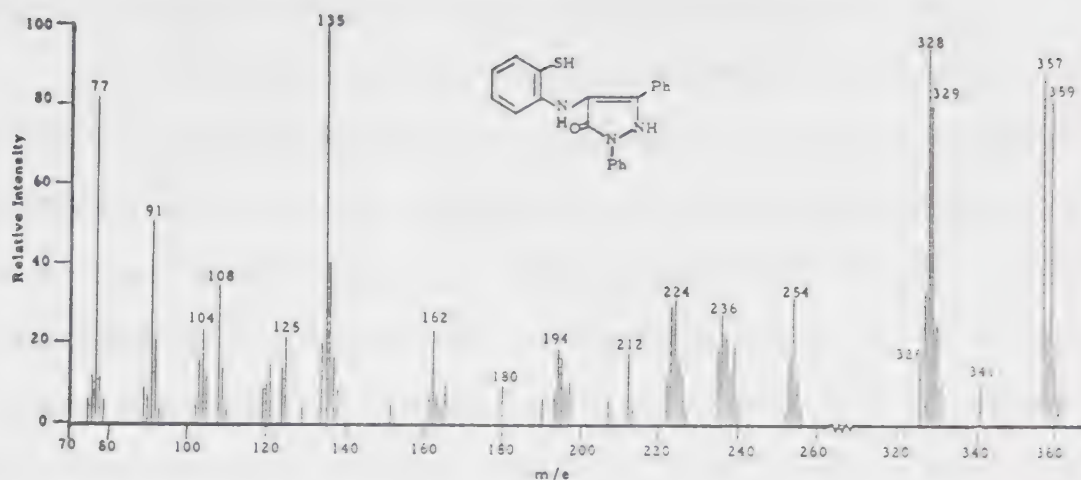
Fig. 14: A portion of the mass spectrum of 1,3-diphenyl-4-(2-mercaptophenylamino)-3-pyrazolin-5-one (417).

methyl analog (406) (Scheme 22, p. 171).
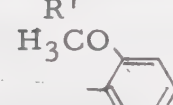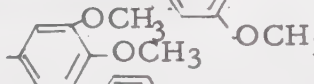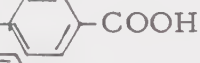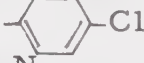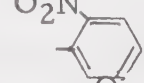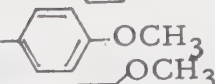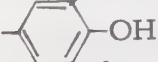
The spiro-benzothiazoline (418) was obtained only in minor quantities during crystallization of the thiol (417), but it was isolated in a good yield when (417) was treated with cold acetic acid. Its identification was based on its correct elemental analysis and its spectral characteristics (i.r., n.m.r. and mass spectrometry), all of which were similar to those observed for the methyl analog (403); the mass spectra of (403) and (418) are discussed later in the mass spectrometry section (part III A).

When reduction of (400b) was performed using zinc and ammonium chloride in aqueous ethanol, the spiro-benzothiazoline (418) was obtained in a good yield. Prolonging the reduction time gave a crude product devoid of the $C = O$ absorption at 1712 cm^{-1} which was believed to be the thiol (417). However, crystallization of this crude product yielded only the spiro compound (418).

Preparation of some spiro(dihydrobenzothiazine)pyrazolones:

When 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) was reacted in refluxing ethanol with different aldehydes and ketones, the expected spiro-dihydrobenzothiazines (419) were isolated in most cases. Identification of these products as spiro-[(3-substituted-3,4-dihydro-2H-1,4-benzothiazine)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5-ones)] (419) was based on their correct elemental analysis as well as their physical and chemical properties. The i.r. spectra displayed N—H stretching and lactam C=O absorption bands similar to those observed with the spiro-tetrahydroquinoline analogs (337). The presence of the C=O absorption bands

(416) + RR'C=O → (419)

	R	R'			R	R'
a,	H	CH$_3$		h,	H	H$_3$CO— OCH$_3$ (with OCH$_3$)
b,	H	C$_2$H$_5$		i,	H	—OCH$_3$ (OCH$_3$)
c,	H	COCH$_3$		j,	H	—COOH
d,	H	Ph		k,	H	—Cl
e,	H	—OH		l,	H	O$_2$N—
f,	H	—OCH$_3$ (OCH$_3$)		m,	H	(furan)
g,	H	—OH		n,	CH$_3$	CH$_3$

around 1700 cm^{-1} suggested cyclized products where the pyrazolone ring can only exist in the "CH" form. This cyclization was confirmed by the lack of solubility of these products (except those possessing acidic substituents) in dilute alkali solutions. In fact, some of these

compounds form hydrochloride salts, though with difficulty. The
n.m.r. spectra of these derivatives also supported the assigned
structures. In addition to the pyrazolone C-3 methyl signal, and
signals ascribable to the aromatic protons and the different substituents
at C-3 of the dihydrobenzothiazine ring, each spectrum contained a
one-proton signal near $\delta 4.8$ ($>$CHR) and another D-exchangeable
NH signal of variable chemical shift. A common feature in most
spectra was the appearance of two signals for both the pyrazolone
C_3-methyl group and the CH group. The separation between these
two signals was as low as 3 Hz (R = p-hydroxyphenyl) and as high as
14 Hz (R = CH_2CH_3). This separation was absent in compound (419n)
where R = R' = CH_3 and also in compound (419c) were R = H and R' = $COCH_3$.
This signal duplication is concluded to be due to the possibility of
mixtures of positional isomers in which the methyl group of the
pyrazolone ring is either in cis or trans position with respect to the
substituent at C-3 of the dihydrobenzothiazine nucleus. However, an
attempt to separate isomers of compound (419l, R = H and R' = o-nitro-
phenyl) by means of fractional crystallization failed.

The mechanism of formation of these dihydrobenzothiazines
(419) is believed to be the same as that suggested earlier for the
formation of the related tetrahydroquinolines. As was noted earlier,
the reaction of the amine (416) with acetone required a longer time
and higher reaction temperature. The reaction with formaldehyde
produced an oil which was difficult to purify. The i.r. spectrum of
this product showed a C=O absorption band at 1710 cm^{-1} but no NH
or OH absorptions were present. This was not investigated further.

The mass spectra of some of these compounds (419) were

recorded (Figs. 15 and 16) and some tentative fragmentation pathways are suggested in Scheme 30. Attempts to deuterate one of the simple derivatives failed but it proved possible to partially deuterate compound (419i). This, in addition to accurate mass measurements (Table 4) of some of the fragment ions in (419d) was helpful in accounting for the fragmentation pattern observed.

Table 4. Accurate Mass Measurement Data of some of the Important Ions in the Mass Spectrum of the Spiro-(dihydrobenzothiazine)pyrazolone (419d).

Measured m/e	Composition	Required m/e	Designation*
352.1447	$C_{23}H_{18}N_3O$	352.1449	c or c'
212.0532	$C_{13}H_{10}NS$	212.0534	d or d'
181.0889	$C_{13}H_{11}N$	181.0892	g
121.0109	C_7H_5S	121.0111	h

* as in Scheme 30.

Unlike the spiro-benzothiazoline derivatives (431) (part III A), most of the fragmentation pathways demonstrated here took place in the dihydrobenzothiazine nucleus rather than in the pyrazolone ring. Some similarities with the fragmentation of the spiro-tetrahydroquinoline derivatives (p. 148) were apparent although in this case more fragment ions were observed which presumably is due to the ability of the sulfur atom to localize the positive charge. With only one exception (419c, R=H and R'=COCH$_3$), these compounds displayed strong molecular ions which, in many cases, were the base peaks in the spectra. The loss of a hydrogen atom (R in all compounds except

419n) or the other substituent in the form of a radical from the C-3

position of the benzothiazine ring gave ions of relatively low abundance

(ions a and b respectively). An ion analogous to a was absent from

compound (419n) where R is a methyl group and also from compound

(419c) where the loss of the acetyl substituent as a radical resulted

in the only strong ion in the spectrum.

An interesting fragment ion demonstrated in all the spectra

(although of very low abundance in compound 419c) was due to the

direct loss of an ṠH radical from the molecular ion. That this loss

of the ṠH radical was (at least in part) direct from the molecular ion

was shown by appropriate metastables in all the spectra recorded.

This, however, was not surprising since the loss of a sulfhydryl

radical from cyclic sulfur compounds is a process observed by

several investigators.

Gilbert and Millard (1969) found that phenothiazine (420)

fragments initially by the loss of its sulfur atom either as elemental

sulfur or as ṠH or ĊSH radicals. The origin of the hydrogen atom

lost as an ṠH radical was not clear, but they depicted it as originating

from the ring nitrogen atom producing (421).

(420)   (421)
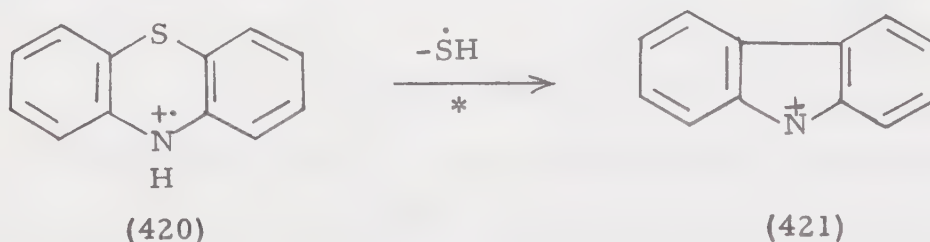
Wahl (1970) also demonstrated the same loss from three

bridged biphenyl derivatives (422), but he gave no explanation of the

origin of the hydrogen atom(s) involved and did not suggest a formula

for the resulting ion. The same investigator found that two bis-
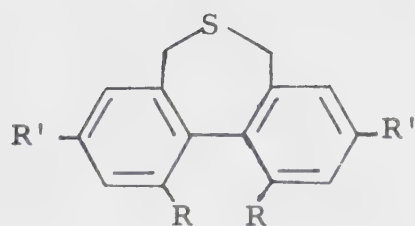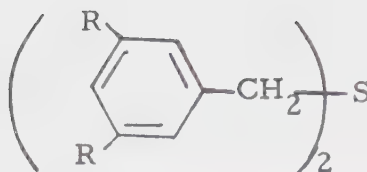
(422) (423)

benzylic sulfides (423) closely related to the bridged biphenyl (422)

showed only very minor losses of SH radicals [0.4-2% of the molecular

ion compared with 55-80% in case of compounds (422)] .   On the other

hand, alkyl aryl sulfides such as (424) gave strong M-33 ions resulting

from the expulsion of SH˙ radical from the molecular ion (Tatematsu

et al, 1966).   A study of the deuterated thioether (424, SCD$_3$ replaces

SCH$_3$) indicated that one third of the hydrogen atoms of the S̄H radical

eliminated were derived from the benzene ring (Scheme 27).
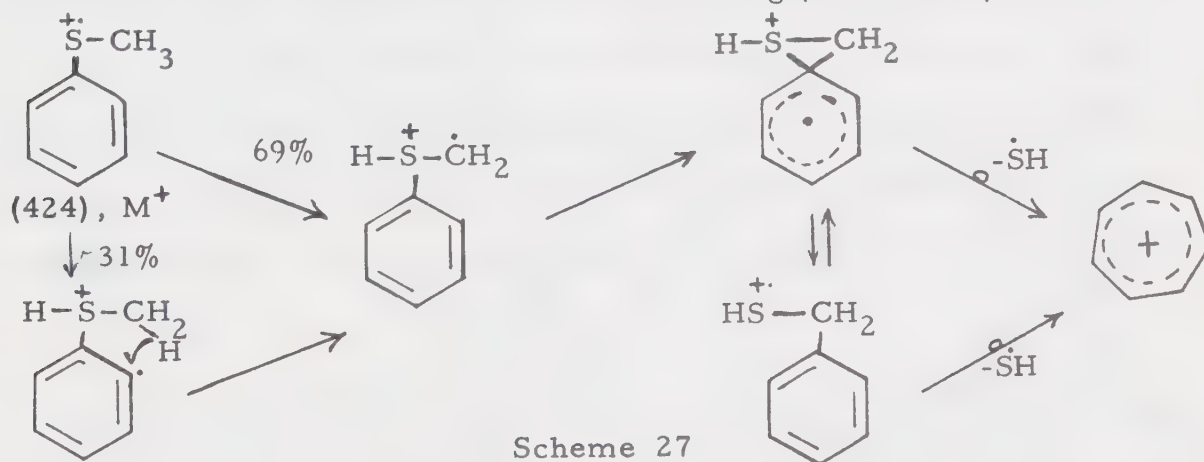
Scheme 27

        In the present study, an attempt to account for the origin of

the hydrogen(s) involved in the ˙SH loss was undertaken.   Deuteration

of the N-4 hydrogen atom of the benzothiazine ring in compound (419i)

showed that this hydrogen is only partially involved.   The molecular

ion of the deuterated compound fragmented to give ions which corres-

ponded to (M-33)$^+$ and (M-34)$^+$.   The mechanism illustrated in

Scheme 28 may explain how such losses could occur. The hydrogen
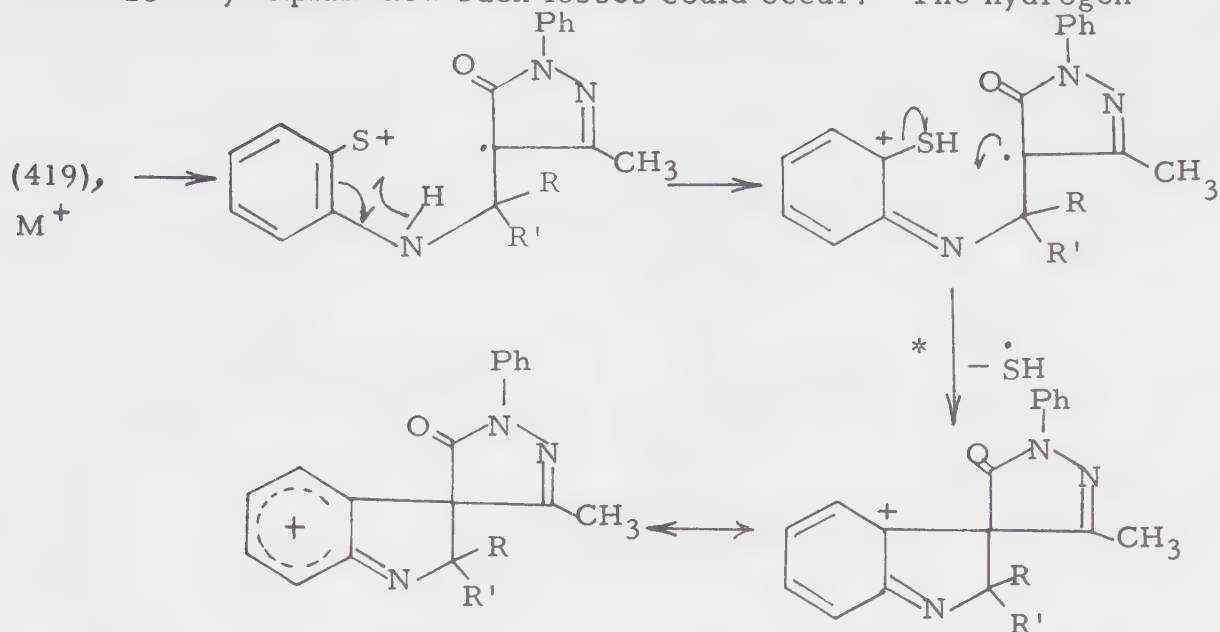
Scheme 28

atom at C-3 of the benzothiazine ring may also be involved in the man-

ner shown in Scheme 29. It may be of significance that in the spectrum

of compound (419n) where C-3 is disubstituted with two methyl groups,

an (M-33) ion was present in the spectrum although its relative abun-

dance (4%) was much less than in the related compounds (e.g. 15% in

419a). No attempt was made to detect the involvement of any other

hydrogens (e.g. of the aromatic ring) in the formation of an ŚH radical

Scheme 29
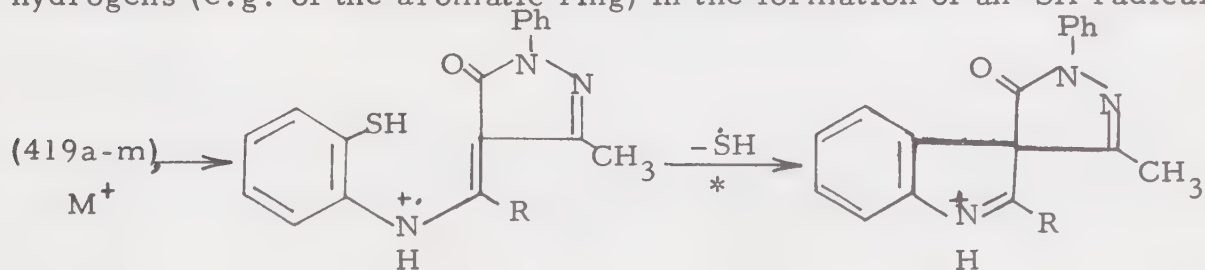
but it is believed that these may also take part in a manner similar to

that shown earlier by Tatematsu et al (1966) in their studies on thio-

ethers.

Another common fragment ion present in all the spectra
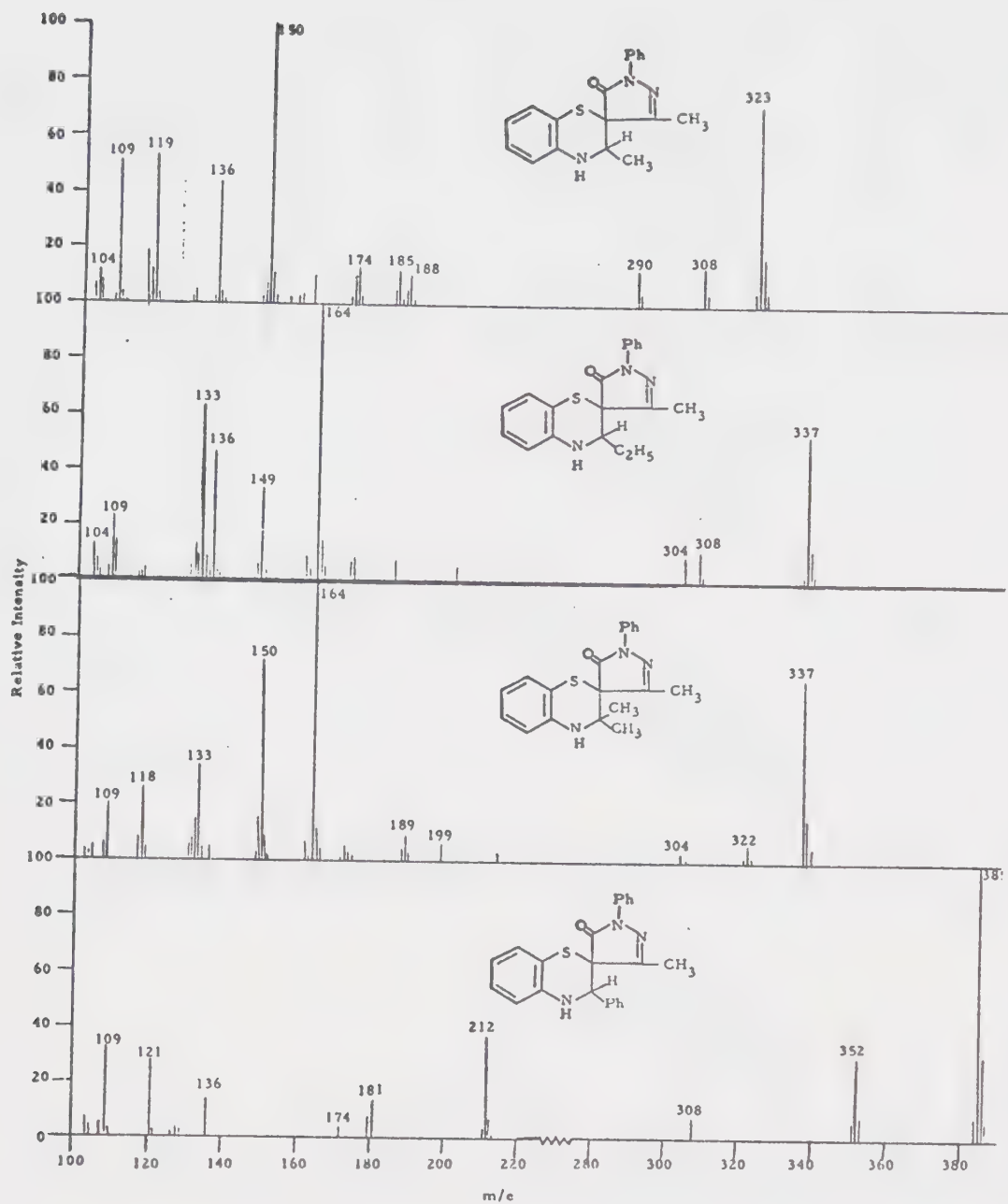
Fig. 15: Portions of the mass spectra of the spiro(dihydrobenzo-thiazine)pyrazolones (419a, b, n, d).
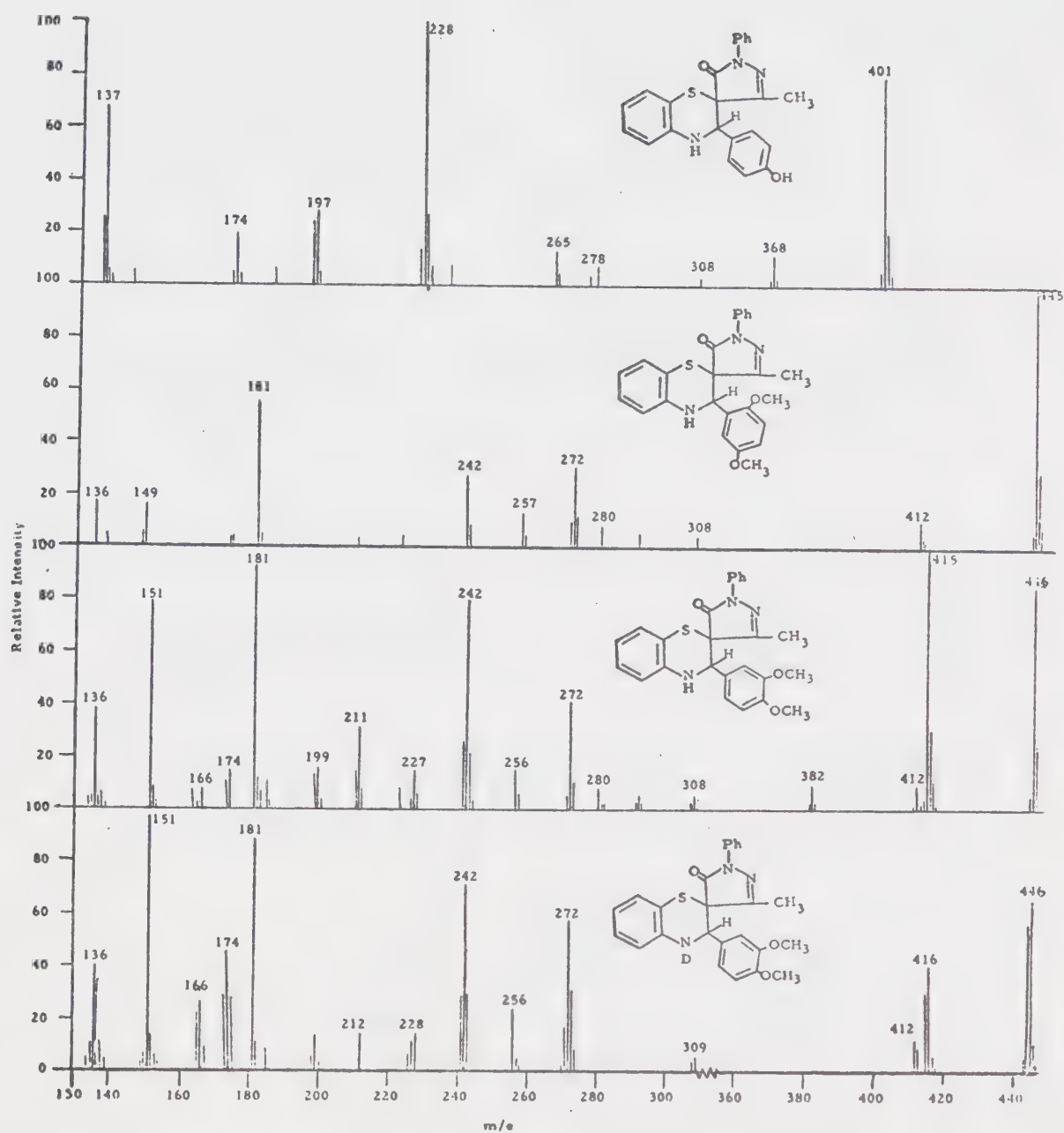
Fig. 16: Portions of the mass spectra of the spiro(dihydrobenzothiazine)-pyrazolones (419e, h, i) and the deuterated derivative of (419i).

Scheme 30

was the ion postulated as $\underline{d}$ or $\underline{d}'$ which resulted from the expulsion of a pyrazolone radical from the molecular ion. A similar ion was also demonstrated in the mass spectra of the tetrahydroquinoline derivatives (337) although in the dihydrobenzothiazines (419) no meta-stables were found to support its direct formation from the molecular ion. Also here, deuteration of compound (419i) indicated that the hydrogen atom at N-4 of the benzothiazine ring was the one mainly involved in the loss of the pyrazolone radical (Scheme 31) since 174 mass units were lost from the molecular ion of the deuterated com-

(419); M^+

$\underline{d}'$
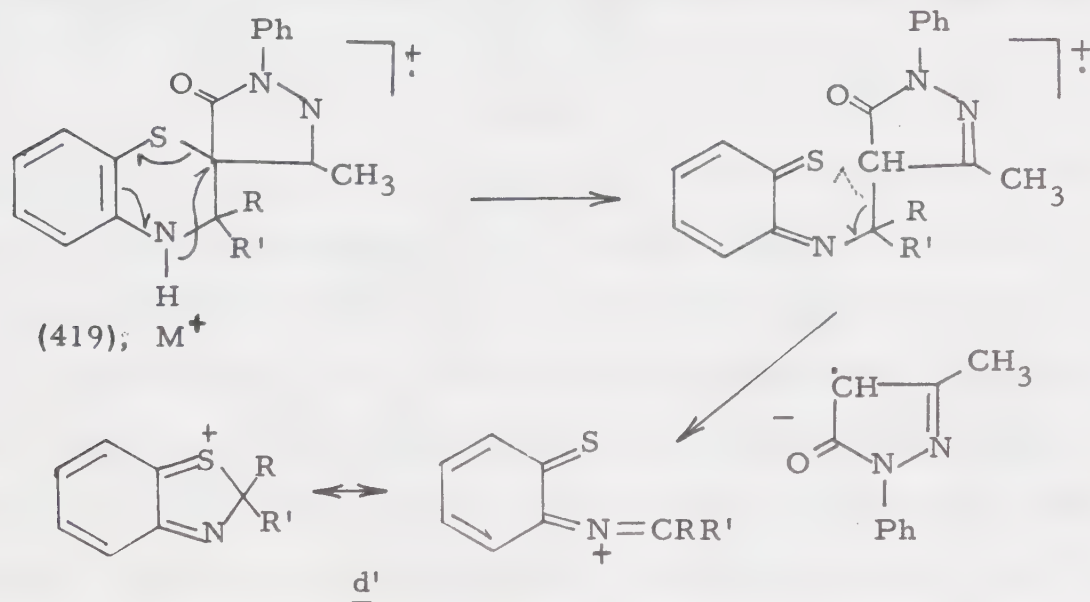
Scheme 31

pound (419i, D replaces H) instead of the 173 mass units expelled from the molecular ion of (419i). Some expulsions of 173 mass units were also demonstrated in the same deuterated compound which might suggest the involvement of the hydrogen atom at C-3 (Scheme 32). However, incomplete deuteration or D→H exchange in the mass spectrometer may account for such loss.

The mass spectrum of the 2,2-dimethyl compound (419n) showed a strong M-173 ion (the base peak) which adds evidence to the
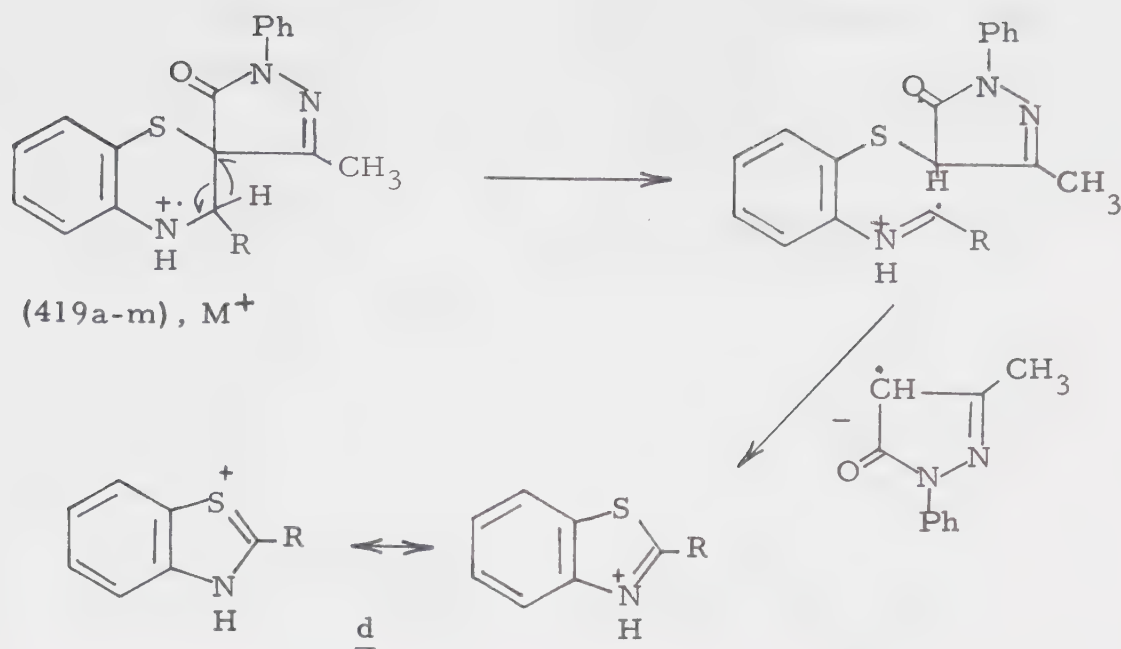
Scheme 32

proposed involvement of the amine hydrogen in the formation of this ion. Another strong ion at m/e 150 in the spectrum of the same compound (419n) is formulated as ion d (R=CH$_3$) although the mechanism of its formation from the molecular ion is obscure. An ion at m/e 136 was found in variable intensities in all the spectra of (419a-m). This ion which is designated as e (Scheme 30) is presumably formed either from the molecular ion or from the fragment ion b. Its formation must involve complex rearrangements, and no speculation on such rearrangements is warranted.

The (M-173) ion (d or d') fragmented further by the expulsion of an R $-$ C$\equiv$N molecule to give the ion f, m/e 109; this expulsion was supported by the presence of appropriate metastable ions. Another major ion in all the spectra which is designated in Scheme 30 as ion g is believed to be formed directly from the molecular ion by expulsion of 204 mass units. Its identification as RR'C$_7$H$_5$N was supported by an accurate mass measurement of the ion

at m/e 181 in the spectrum of compound (419d) (Table 4).   The

formation of this ion can be explained as follows:
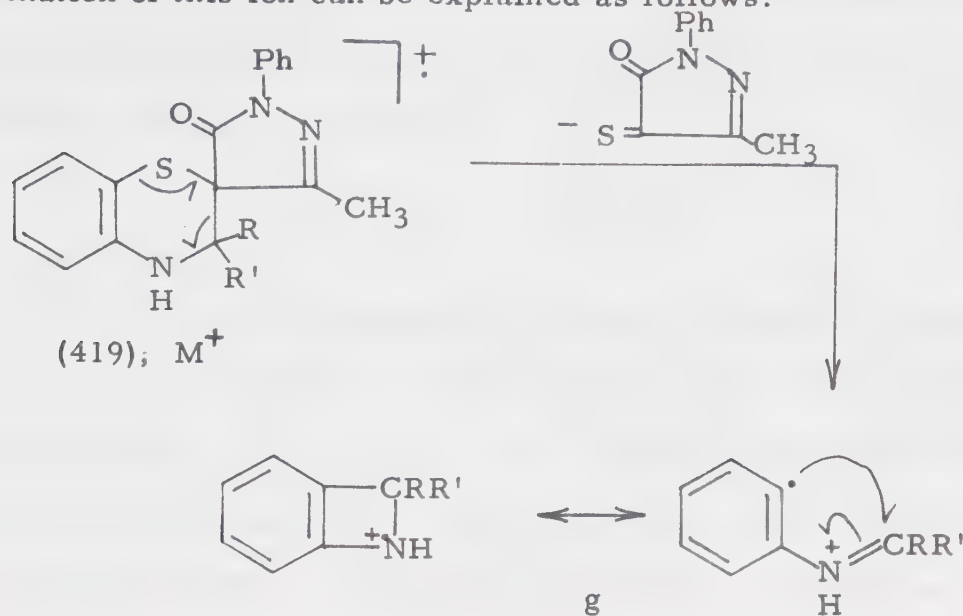
Scheme 33

An ion corresponds to the formula R—C≡S+ as shown by
accurate mass measurement of the ion at m/e 121 in compound (419d)
was only demonstrated in the spectra of the derivatives in which R was
an aromatic system.   Apparently it is derived from ion d though no
metastables were present in support of this suggestion.

In addition to these common fragmentation pathways some
other strong ions were present which resulted from the fragmentation
of the substituent at C-3 of the benzothiazine ring.   The $(M-COCH_3)^+$
ion in case of compound (419c) has already been mentioned.   This was
the only case in which the loss of the substituent at C-3 gave rise to a
very strong fragment ion leaving the other fragments only minor.
Compound (419i) in which R =H and R'=3,4-dimethoxyphenyl demon-
strated strong frament ions at m/e 415, m/e 242 and m/e 151 which
resulted from the expulsion of CH_2O molecules from the molecular
ion and from ions d and h respectively.   It is interesting to note that

although these ions were the strongest in the spectrum of (419i), the isomeric compound (419h) in which R =H and R'=2,5-dimethoxyphenyl did not produce any ions at m/e 415 or m/e 151 and gave only an ion of medium intensity at m/e 242.

— — — —

4-(2-Aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) could be condensed with both salicylaldehyde and p-hydroxy-benzaldehyde but whereas the product with the latter aldehyde was the dihydrobenzothiazine (419e), salicylaldehyde reacted with (416) to give a yellow crystalline product which is tentatively identified as the Schiff base (425a). A related product (425b) was obtained when 2,4-dihydr-oxybenzaldehyde was reacted with the amine (416). It appears,

(419e)

(425)   a, R =H
         b, R =OH
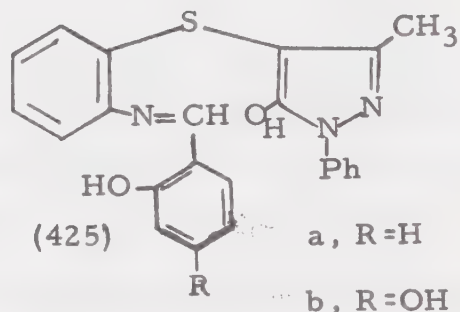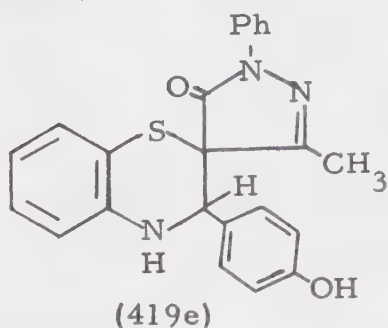
therefore, that the amine (416) reacts with o-hydroxybenzaldehydes in the same manner as described earlier for 4-(2-aminobenzyl)-1,3-diphenyl-5-pyrazolone (321b).

The Schiff base structure (425) was suggested by the elemental analyses of both products ($C_{23}H_{19}N_3O_2S$ and $C_{23}H_{19}N_3O_3S$ for (425a) and (425b) respectively) and by the similarity of their i.r. spectra to those of compounds (385) (see p. 152). Medium intensity absorption bands were present at 1612 cm^{-1} (425a) and at 1610 cm^{-1}

(425b) and are assigned to the imine C=N group (c.f. Cloughetry et al, 1957). The n.m.r. spectra of (425a,b) also agreed with the Schiff base structure. In addition to the methyl and aromatic signals, a one proton =CH signal was located near δ5.4 and D-exchangeable signals ascribable to the OH groups were observed in the spectra. The mass spectrum of (425a) (Fig. 17) was similar to the spectra of the spiro-dihydrobenzothiazines (419) although it differed in the relative intensities of the fragment ions formed. The ions at m/e 174
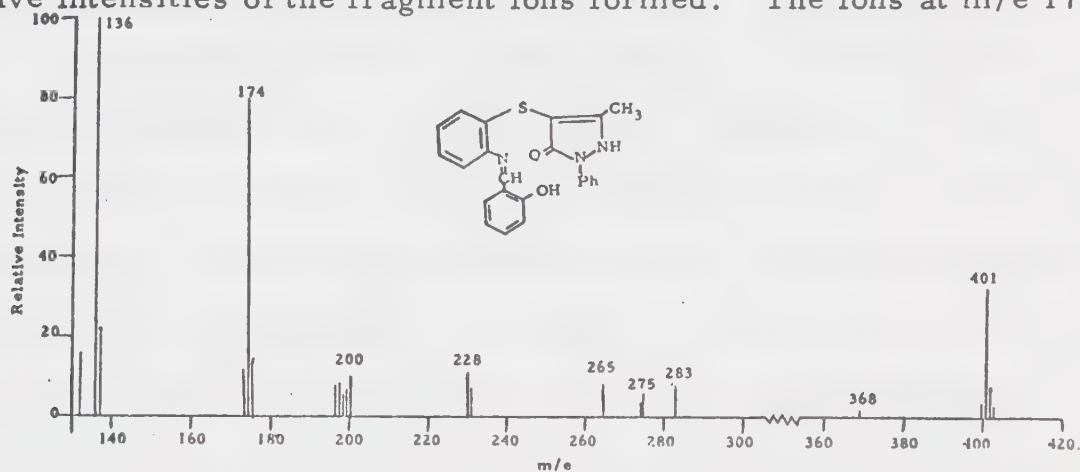
Fig. 17: A portion of the mass spectrum of 4-[2-(o-hydroxybenzyli-dene)aminophenylthio]-3-methyl-1-phenyl-3-pyrazolin-5-one (425a).

($C_{10}H_{10}N_2O$) and at m/e 136 (C_7H_6NS), for which structures (426) and (427) are suggested, are the strongest in the spectrum of (425a) but only present in weak or medium abundance in the dihydrobenzothiazines (419). On the other hand, the M-33 and M-173 ions are much weaker
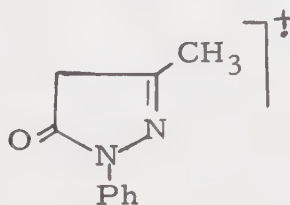
(426), m/e 174
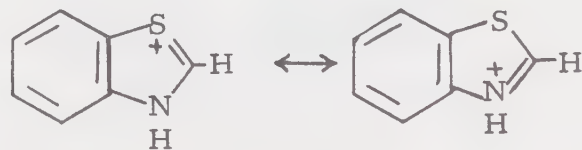
(427), m/e 136

in (425a) than in the cyclized compounds (419). No fragment ions were found in the spectrum of (425a) due to the fission at the ring-carbon, or ring-nitrogen bonds of the imine group. This contrasts with behavior

of other Schiff bases (Elias and Gillis, 1966; see p. 152 of this thesis).

The ease of solubility of compounds (425) in dilute sodium hydroxide was not very helpful in confirming the presence of an enolizable hydrogen in the pyrazolone nucleus since phenolic functions were also present. However, determination of the number of acidic hydrogens in compound (425a) indicated the presence of two phenolic and/or enolic groups in this molecule in accordance with the non-cyclized structure (425a).

Attempts to prepare a methyl derivative of (425a) by the use of dimethylsulfate or diazomethane failed. Reduction of (425a) using sodium borohydride in aqueous dioxane did not produce identifiable products. Acetylation of (425a) with acetic anhydride produced a diacetate, $C_{27}H_{23}N_3O_4S$ (M$^+$, m/e 485). Similarities between the i.r. spectrum of this compound and that of the diacetate (428) suggested that both compounds were structurally related. The i.r. spectrum of each displayed an ester $C=O$, a lactam $C=O$ and an amide $C=O$ in the form of a doublet. These spectra were similar to those of the diacetylated derivatives (391), (392) and (394) (see p. 156)

(428)

(429)
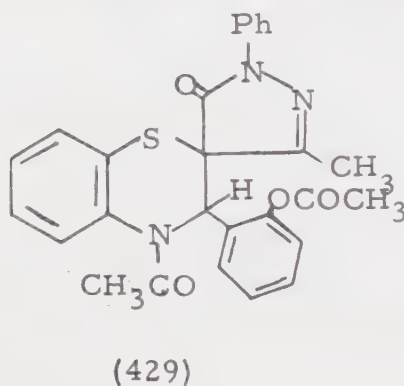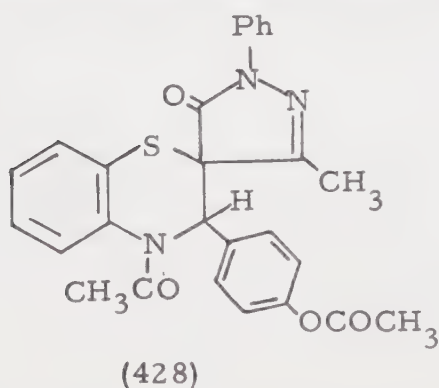
except that the amide $C=O$ absorption appeared as a single band in the latter compounds. The n.m.r. spectra of (428) and diacetylated (425a) were also very similar. In both, the pyrazolone methyl signals were

located far upfield (at δ 0.98 and δ 1.03) as found earlier for other

acetylated dihydrobenzothiazines and tetrahydroquinolines (p.137).

Based on these data, the diacetate product obtained from (425a) was

assigned the cyclic structure (429). The mass spectrum of the

diacetylated product (Fig. 18) supported this cyclized structure (429).

It had a strong molecular ion which initially lost two ketene molecules

to give an ion which fragmented further in a manner similar to that

observed with the spiro-dihydrobenzothiazines (319).
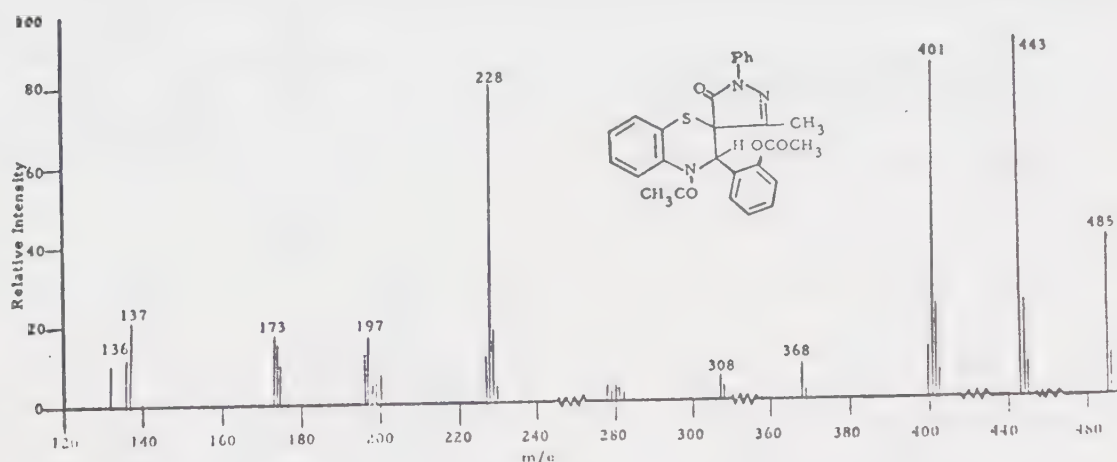
Fig. 18: A portion of the mass spectrum of spiro{[4-acetyl-3-(o-acetoxyphenyl)-3,4-dihydro-2H-1,4-benzothiazine]-2,4'-[3'-methyl-1'-phenyl-1H-pyrazolin-5'-one]} (429).

Part III: MASS SPECTROMETRY

(A)   The Mass Spectra of Some Substituted Pyrazolone Derivatives

         Four types of spiro-pyrazolones have been prepared and
characterized in this present study.   These are derivatives of spiro-
[(indoline)-2,4'-(pyrazolin-5'-one)] (430), spiro[(benzothiazoline)-
2,4'-(pyrazoline-5'-one)] (431), spiro[(pyrazolin-5-one)-4,3'-
(tetrahydroquinoline)] (337) and spiro[(2,3-dihydro-4H-1,4-benzo-
thiazine)-2,4'-(pyrazolin-5'-one)] (419).   Many of these compounds

(430)   (431)

(337)   (419)
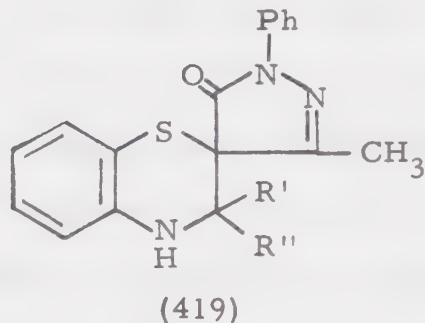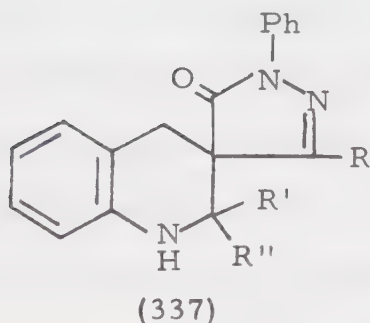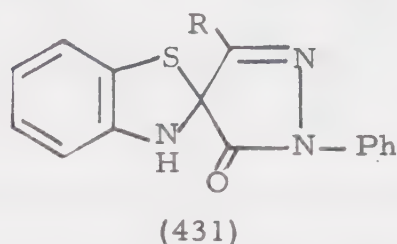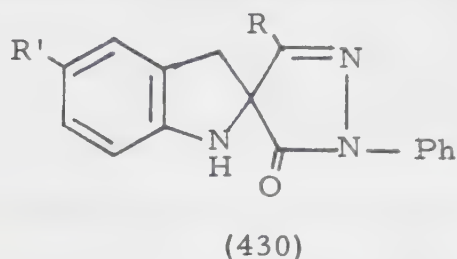
were characterized by their mass spectra.   It was noted that, in
compounds (430) and (431), fission occurred mainly in the pyrazolone
nucleus and produced the major fragment ions in the spectra.   A
literature search revealed two recent studies on the mass spectra of
some simple pyrazolone drivatives (Desmarchelier and Johns, 1969b)
and some substituted pyrazolone azomethine dyes (Maier et al, 1969)
but no spiro-pyrazolones have been investigated.

         Although structurally related, the spiro(tetrahydroquino-
line)pyrazoles (337) and the spiro(dihydrobenzothiazine)pyrazolones
(419) fragmented differently from the spiro(indoline)pyrazolones (430)

and the spiro(benzothiazoline)pyrazolones (431). The first two
classes of compounds did not exhibit any major fragments which were
derived from cleavage of the pyrazolone nucleus; rather fragmenta-
tion in the other part of the molecule occurred and the pyrazolone
nucleus was expelled from the molecular ions as a radical. In
contrast, the spectra of the 4-(2-aminobenzyl)pyrazolone derivatives
(321) and their sulfur analog (416) contained relatively strong ions

(321)   Ph   (416)   Ph
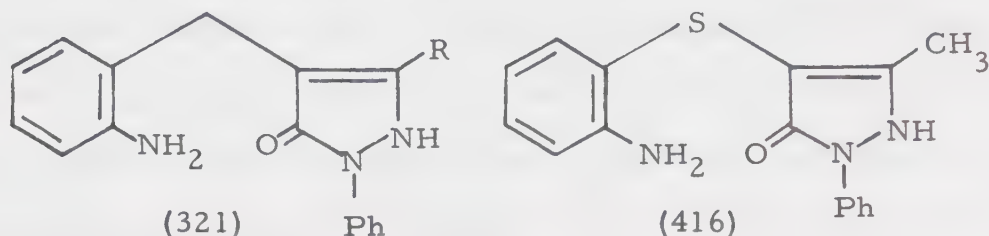
corresponding to the pyrazolone nucleus, but these ions did not frag-
ment further to any appreciable extent. Accordingly, the spectra of
these two amines (321) and (416) and the spiro-pyrazolones (337) and
(419) were discussed separately earlier in this thesis. Similarities
and differences between the spectra of these compounds and those now
discussed in detail will be pointed out whenever there is a necessity.

      In addition to the spiro-pyrazolones (430 and 431) spectra,
the mass spectra of the parent pyrazolone derivatives (317), (329) and
(330) were recorded and interpreted. The spectrum of one of these
compounds, 3-methyl-1-phenylpyrazoline-5-one (317a), was recorded

(317)   a, R=CH$_3$ (329)

       b, R=Ph
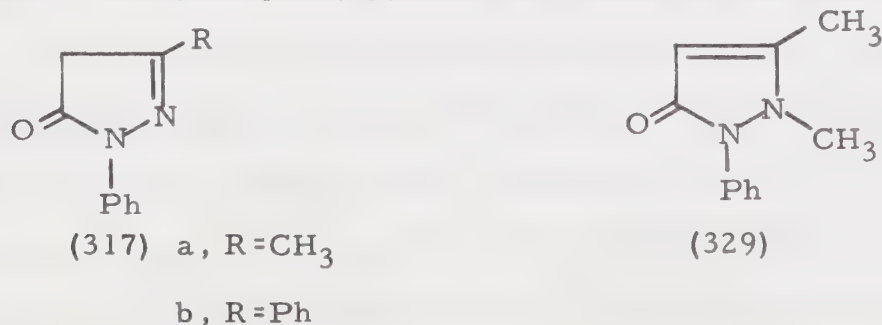
by Nishiwaki (1967) but its modes of fragmentation were not completely
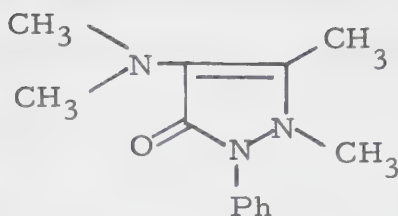
(330)

interpreted.   Spectra of the two N,N-disubstituted pyrazolone deriva-
tives, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one(antipyrine)(329) and
2,3-dimethyl-4-dimethylamino-1-phenyl-3-pyrazolin-5-one (aminopyrine)
(330) have been published (Tatematsu and Goto, 1965) but their frag-
mentation pathways were not discussed.   These two compounds, in
addition to their usefulness as models for the N,N-disubstituted pyra-
zolones, are also of medicinal interest and are present in some
pharmaceutical preparations.

From the pyrazolone derivatives examined, those which
are 5,5-disubstituted or which are N,N-disubstituted, have "fixed"
structures and no tautomerism is possible.   The others e.g. (317)
can exist theoretically in one or more of the three possible tautomeric
forms which were discussed earlier.   For these derivatives
with mobile hydrogen atoms, the tautomeric forms in the solid state
were determined in order to see whether, or not, such tautomerism
in the ground state would be reflected in their mass spectral behavior.

The mass spectra of the four pyrazolones (317a and 317b),
(329) and (330) are shown in Figs. 19 and 20 and their suggested frag-
mentation patterns are illustrated in schemes 34, 36 and 37.   It was
shown earlier in this study that the two pyrazolones (317) exist in the
solid state either in the enol "OH" form or, according to Katritzky
and Maine (1964), in strongly bonded NH-form in which proton transfer

(to give the OH-form) probably takes place. On the other hand, compounds (329) and (330) exist only in the NH-form.

$$(317\text{-OH}) \rightleftharpoons (317\text{-NH})$$

While the two pyrazolones (317a and 317b) displayed similar fragmentation pathways, each of the N,N-disubstituted derivatives (329) and (330) showed a unique behavior and both demonstrated some unusual modes of decomposition under electron impact. The high degree of stability of these oompounds, as well as most of the other pyrazolone derivatives studied was indicated by the strong molecular ions displayed which were, in most cases, the strongest ion in the spectra.

Several initial cleavages were demonstrated in the spectra of (317a) and (317b) but only two of these gave rise to prominent fragment ions (Scheme 34). The direct expulsion of a ketene molecule $(CH_2{=}C{=}O)$ from the molecular ions of both compounds gave rise to relatively strong ions (a). Also the fragment ion at m/e 105 (b) was prominent in both spectra; this ion which was attributed to the phenyl diazonium cation $(PhN_2)^+$ is believed to originate directly from the molecular ion and from the $(M\text{-}CO)^+$ ion (c) since strong supporting metastables were present at appropriate m/e values. The possibility of contribution by isobaric ions $(PhNCH_2)^+$ or $(PhCO)^+$, the latter of which could be formed by a phenyl migration, was considered but accurate mass measurement of this m/e 105 ion in the spectrum of (317a) revealed that it was solely due to $(PhN_2)^+$.

Other minor pathways in the spectra of (317a) and (317b) are the expulsion from the molecular ions of a phenyl diazonium $(PhN_2^{\bullet})$ and a formyl $(^{\bullet}CHO)$ radical and a carbon monoxide (CO) molecule; the last two losses are supported by metastable ions at m/e 120.8 and m/e 122.5 in (317a) and at m/e 181.65 and m/e 183.32 in (317b)*.

The expulsion of $HN_2^{\bullet}$ or $RN_2^{\bullet}$ radicals from the molecular ion was shown to be the major initial pathway in the spectra of the pyrazolones studied by Desmarchelier and Johns (1969b). However, in compounds (317a) and (317b), this was shown to be only a minor fragmentation (3% and 1% respectively) which was followed by the expulsion of a CO molecule to produce the ion (f). This ion (f) could also arise by the loss of a $PhN_2^{\bullet}$ radical from the $(M-CO)^+$ ion. The strong peak at m/e 103 in compound (317b) which is attributed to a $(CH_2{=}\overset{+}{C}{-}C_6H_5)$ species (ion f where $R{=}C_6H_5$) is especially strong due presumably to the stability offered by the aromatic ring in this ion.

The ion at m/e 105 (b) decomposes further by the loss of a nitrogen molecule to form the $(C_6H_5)^+$ species (i). The origin of the ion at m/e 91 which corresponds to the species $(C_6H_5N)^+$ was not

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*   In a recent communication published after this work was completed, Larsen et al (1973) examined the mass spectrum of (317a) and suggested a non-cyclic structure (432) for the $(M-CO)^+$ ion at m/e 146. Structure (433) was suggested for the ion at m/e 145 $(M-HCO)^+$. This suggestion was based on the finding that both the hydrogen atoms at C-4 were retained in the $4,4-d_2$ analog and the ion shifted to m/e 147.

(317a), $M^{\ddagger}$ $\xrightarrow{-CO}$ (432), m/e 146 $\xrightarrow{-H^{\bullet}}$ (433), m/e 145

m/e 174
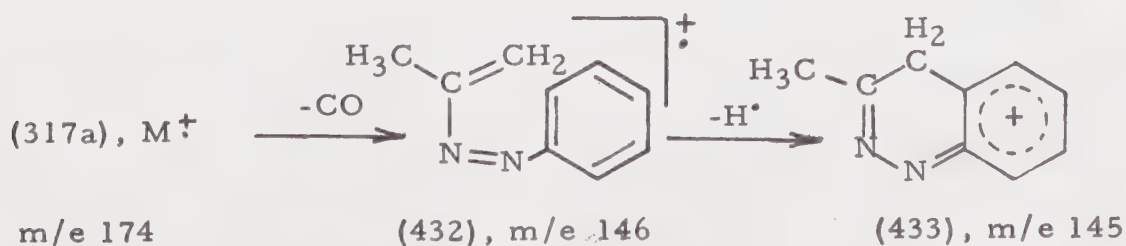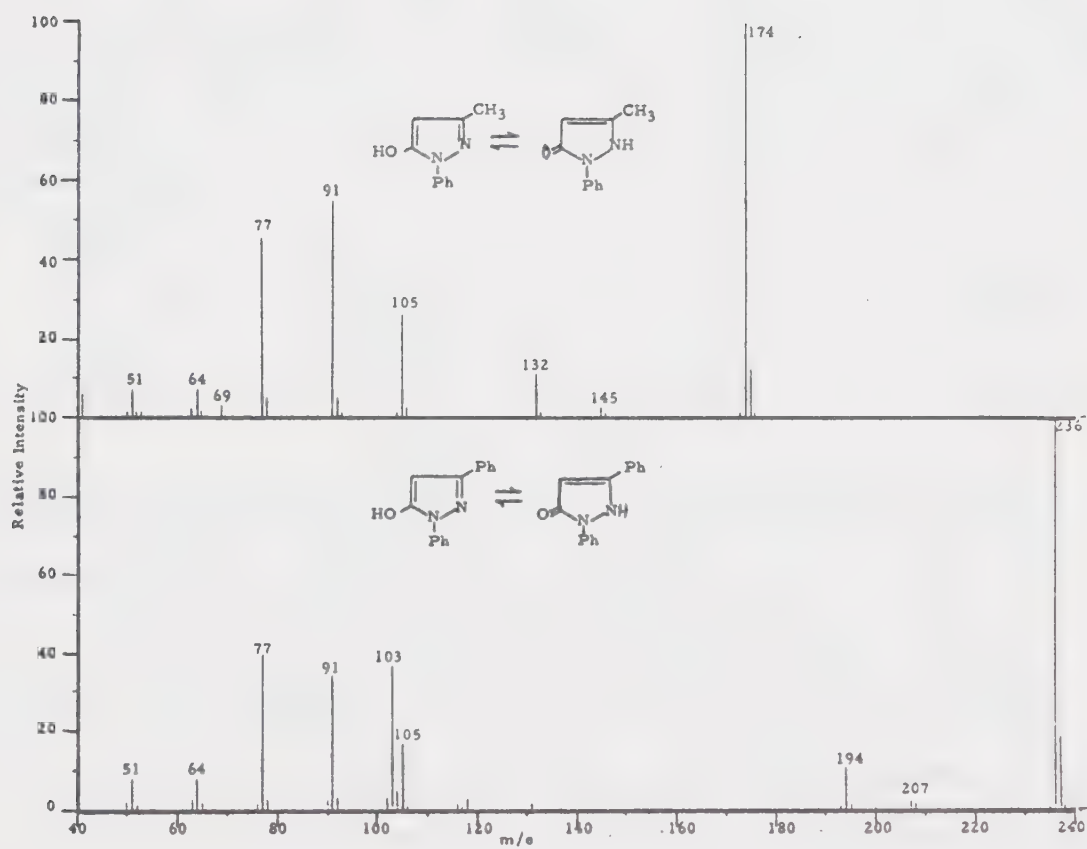
Fig. 19: Portions of the mass spectra of 3-methyl-1-phenyl-2-pyrazolin-5-one (317a) and 1,3-diphenyl-2-pyrazolin-5-one (317b).
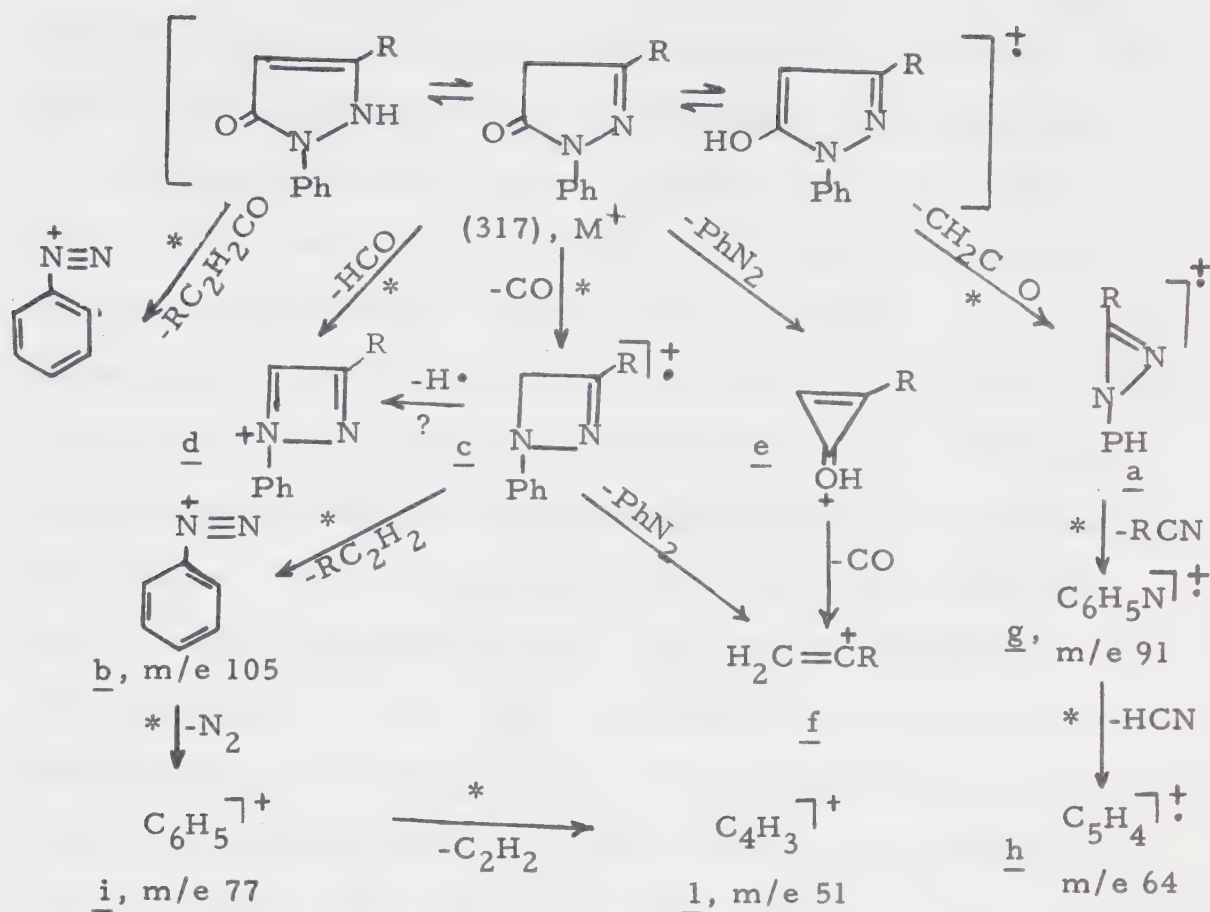
Scheme 34

accounted for by Nishiwaki (1967) when he studied the mass spectrum of compound (317a). The presence of metastables at m/e 62.73 and m/e 42.7 in the spectra of (317a) and (317b) respectively, suggested that this ion ($\underline{g}$) originates from the (M-42)$^+$ ion ($\underline{a}$) by the expulsion of either a CH_3CN or C_6H_5CN molecule. These observations indicate that an N—N bond cleavage occurs in these pyrazolones. The cleavage of such N—N bonds in compounds containing two or three linked nitrogen atoms, has been the subject of studies in many laboratories. In hydrazine (Dibeler et al, 1959), diazirine (Graham, 1962), 2,5-di-phenyl-1,3,4-oxadiazole (Cotter, 1964) and indazolones (Desmarchelier and Johns, 1969a) this cleavage was found to be difficult. On the other hand, such N—N bond fission is an important fragmentation process in

hydrazones (MacLeod et al, 1966), semicarbazones (Becher et al, 1966) and sulfonyl hydrazones (Bhati et al, 1966).   Thuÿl et al (1970) reported that the cleavage of the N—N bond and expulsion of HCN is the predominant process in the mass spectra of pyrazoles while Desmarchelier and Johns (1969b) found no evidence for initial N—N cleavage in pyrazolones.   Earlier, Nishiwaki (1967), in his study of the mass spectra of pyrazoles (which included the pyrazolone (317a), reported an N—N cleavage but concluded that the initial cleavage of this bond is likely to be supressed in cases where the nitrogen is substituted.   However, this was not the case with the compounds studied in the present investigation, which are all substituted at one or both nitrogens.   Apart from the example already mentioned which demonstrated N—N bond cleavage and expulsion of CH_3CN or C_6H_5CN molecules from the $(M-42)^+$ ion in (317a) and (317b), evidence for initial cleavages of this linkage was found in the spectra of antipyrine (329), aminopyrine (330) and the spiro-pyrazolones (430) and (431).

The antipyrine (329) spectrum had a strong ion (84%) at m/e 96 which was second in abundance only to the base peak (the molecular ion).   An accurate mass measurement of this ion revealed that it was a singlet which had the formulation C_5H_6NO.   The presence of a strong metastable at m/e 49.02 suggested that it was formed directly from the molecular ion.   Although clear evidence for the identity of this ion is lacking, it is represented in Scheme 36 as the ion c.   This ring expanded formulation is possibly the best representation for this strong ion since it can account for the subsequent expulsion of a CH_3CN molecule to give the ion d (Scheme 36).   The formation of both these major ions (c and d) as well as the strong ion at

(329), M$^+$, m/e 188 $\underline{c}$, m/e 96
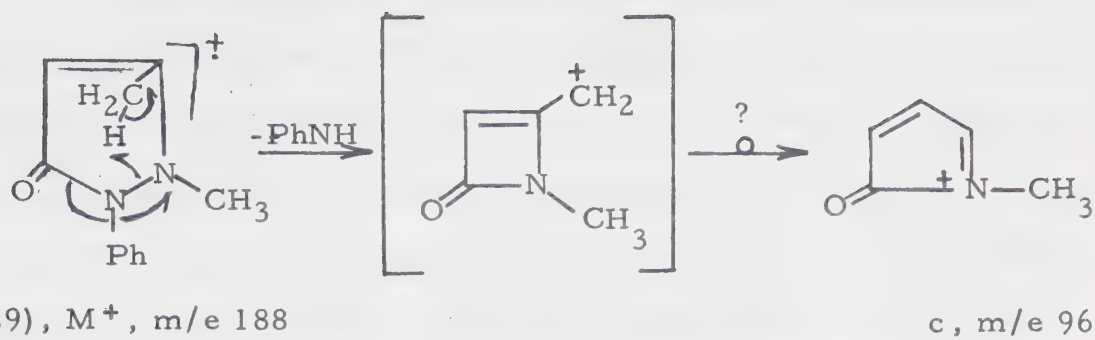
Scheme 35

m/e 56 (ion $\underline{g}$) indicated that N—N bond cleavage does occur as primary
and secondary processes in the mass spectra of pyrazolones expecially
when both nitrogens are substituted.

This same point is also illustrated in the mass spectrum
of aminopyrine (329) where the base peak at m/e 56 is formed by
successive losses from the molecular ion of a C_6H_5NCO molecule,
a $CH_3^{\bullet}$ radical and a CH_3NC molecule (Scheme 37).   All these
transitions are supported by the presence of metastable ions at
appropriate m/e values.   The initial expulsion of a C_6H_5NCO mole-
cule from the molecular ion again supports the possibility of initial
scission of the N—N bond in the pyrazolone nucleus.

A strong ion at m/e 56 ($CH_3N=\overset{+}{C}CH_3 \longleftrightarrow CH_3\overset{+}{N}\equiv CCH_3$)
was also demonstrated in the mass spectra of the pyrazolones (324a)
and (408).   An equivalent ion at m/e 118 was present in the spectrum of
(324b).   The presence of these fragments is probably useful in the
identification of 2,4-disubstituted pyrazolones.

(324)   a, R=CH_3
         b, R=Ph

(408)
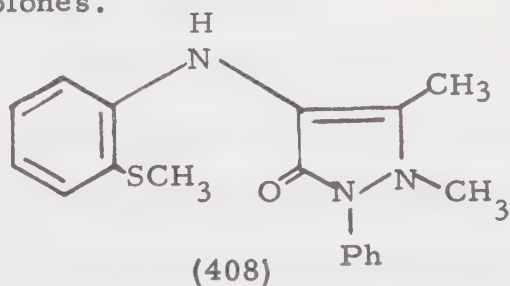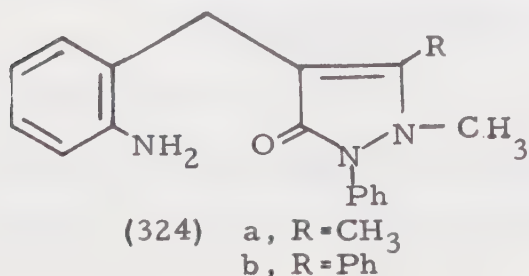
Other important pathways in the spectra of antipyrine (329) and aminopyrine (330) are the expulsion of a hydrogen atom and a methyl radical from their molecular ions. The $(M-1)^+$ ions were stronger than the $(M-15)^+$ ions in both spectra. No conclusive evidence for the origin of the expelled hydrogen atom is available without labelling studies. However, there are some indications that this occurred from the N_2-methyl and not from the C_3-methyl group as was suggested by Desmarchelier and Johns (1969b). This observation is based on the finding that compound (317a), which has a C_3-methyl substituent, showed only a very weak M-1 ion (1%). The same was also noted in the spectra of all the pyrazolones studied in this investigation which had methyl substituents at the 3-position of the pyrazolone ring, while on the other hand, those N_2-methyl substituted pyrazolones such as (324) and (408) demonstrated relatively strong $(M-1)^+$ ions. This is also in accord with the spectra of the pyrazolones reported by Maier et al (1969) which showed, at most, negligible amounts of $(M-1)^+$ ions although most of them had C_3-methyl substituents.

The methyl radical losses in (329) and (330) most likely originate from N_2-methyl rather than from C_3-methyl substituents since no such loss was demonstrated in compound (317a). Also, the presence of a stronger $(M-15)^+$ ion in the spectrum of antipyrine than that in aminopyrine suggests the absence of any considerable contribution from the dimethylamino substituent in aminopyrine.

The expulsion of $PhN_2^\bullet$ radical from the molecular ion was demonstrated in (317a) and (317b) as only a very minor process. This loss was not observed in either antipyrine (329) or aminopyrine (330). However, an analogous loss of a $PhN{=}N{-}CH_3$ molecule was observed
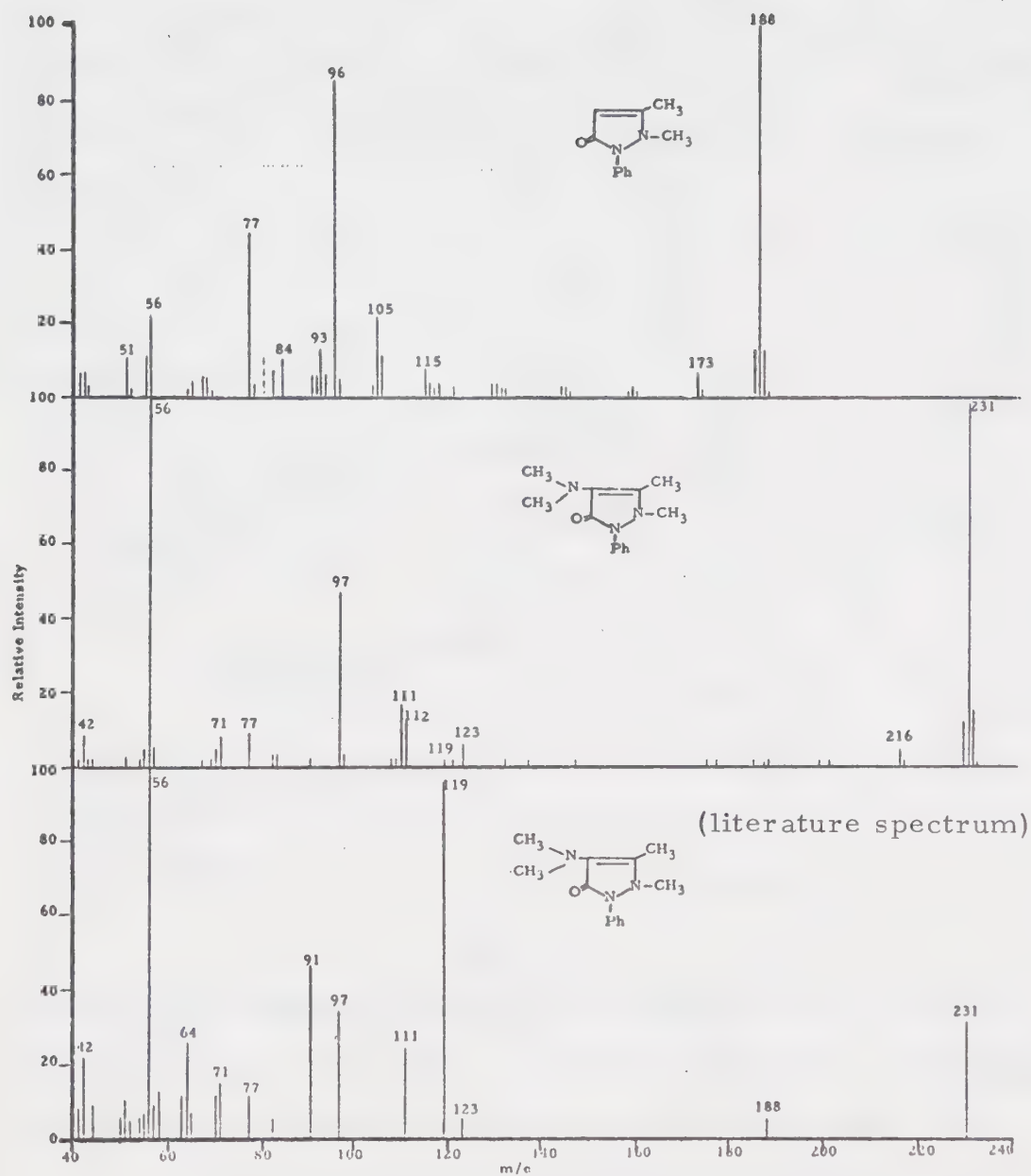
Fig. 20:   Portions of the mass spectra of antipyrine (329) and
           aminopyrine (330).
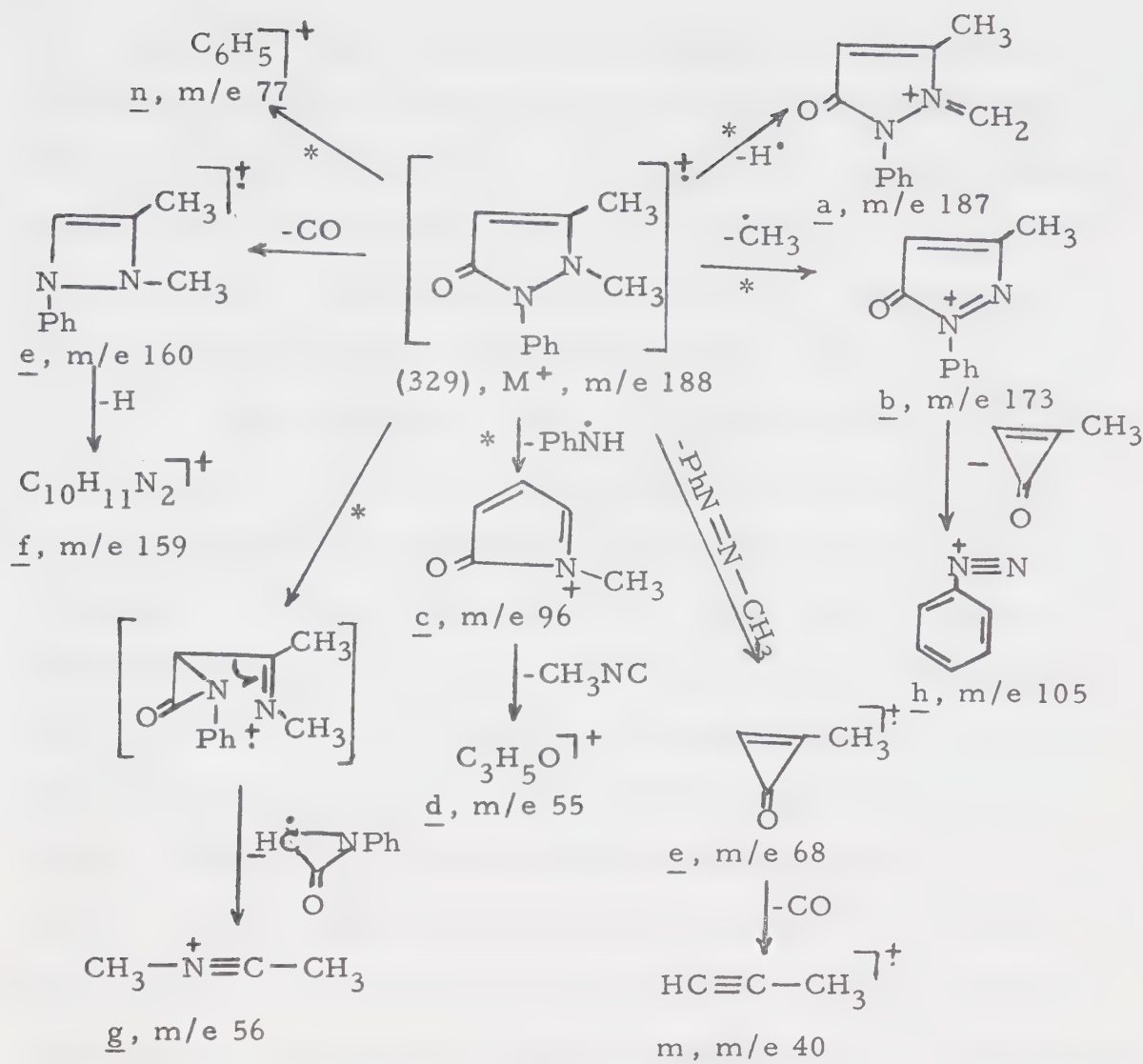
Scheme 36

and led to appreciably abundant ions especially in the spectrum of aminopyrine (m/e 111; 17%). Both these (M-120)$^+$ ions fragmented further by the expulsion of a carbon monoxide molecule.

Another important fragmentation in the spectrum of anti-pyrine (329) was the formation of the phenyl diazonium cation h (Scheme 36) mostly from the (M-CH$_3$)$^+$ ion. Curiously, this was not demonstrated to any extent in the spectrum of aminopyrine in spite of structural similarities with antipyrine. Also, another minor ion (2%) corresponding to the expulsion of a CO molecule from the molecular

ion of antipyrine was not present in the spectrum of aminopyrine.

Similarly, a weak $(M-29)^+$ ion which may be due to the loss of CHO$^•$

radical from the molecular ion or to the loss of H$^•$ from the $(M-CO)^+$

ion was found in the spectrum of antipyrine, but not in the spectrum

of aminopyrine. These findings indicated a lack of correlation

between the fragmentation modes of these two compounds.

Some differences between a reported spectrum (Fig. 20)

of aminopyrine (330) and those recorded here deserve comment.

Tatematsu and Goto(1965) described a spectrum which contained a

strong ion (95% relative intensity) at m/e 119. This ion was only

present in 1% relative abundance under the conditions used in this

study (70 eV and 110°). Changing the temperature did not seriously

affect the intensity of this ion (5% at 165°). A spectrum of amino-

pyrine (330) recorded on a combined gas chromatograph/mass spectro-

meter* was also similar to the spectrum recorded in this study.

Such an ion at m/e 119 may be attributed to the cleavage of the N−N

bond with the formation of the phenyl isocyanate cation. The expulsion

of a CO molecule from this cation could also explain the presence of

a strong ion (46%) at m/e 91 in the spectrum reported by Tetamatsu

and Goto (1965), and which was only 2-4% abundant in three spectra

recorded for the present study.

m/e 119   m/e 91

---
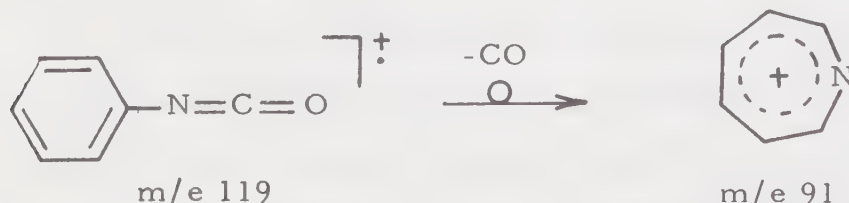
*recorded on a Perkin-Elmer model 270 combined gas chromatograph/
mass spectrometer at Chelsea College, University of London, England.
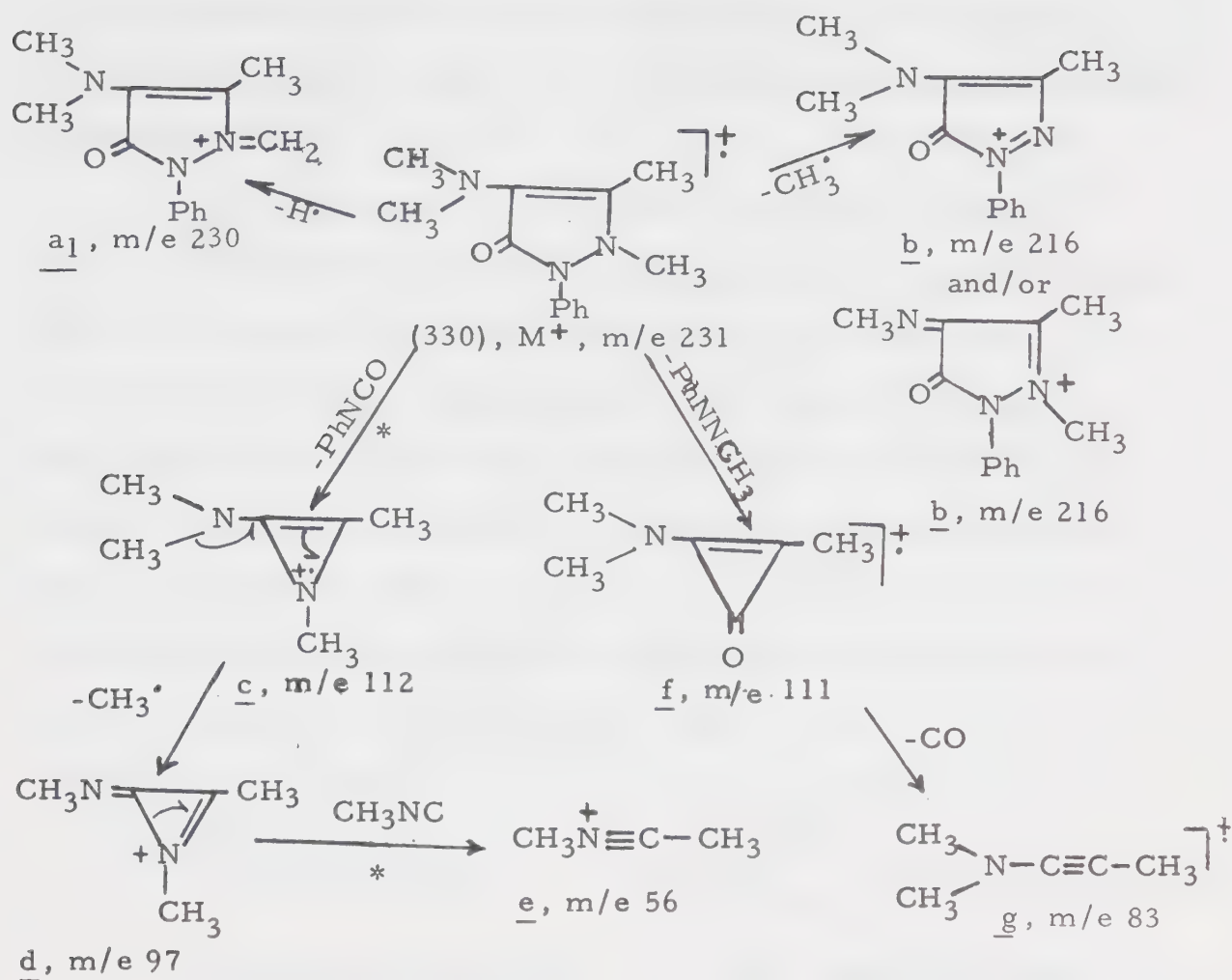
Scheme 37

It is difficult to explain these gross differences except to suggest that aminopyrine fragments by alternative pathways depending on the conditions within the mass spectrometer.

- - - -

The spiro(indoline)pyrazolones (430) and the spiro(benzo-thiazoline)pyrazolones (431) displayed considerable similarities in their behavior under electron impact. However, some differences were also demonstrated either in the fragmentation pathways or in the intensity of the fragment ions produced. These differences are presumably due to the ability of compounds (431) to localize the charge

on the sulfur atom and also due to the contribution of the methylene

protons of the indoline ring in (430) to some of the fragment ions which

are absent in (431).

The mass spectra of five spiro-(indoline)pyrazolone

derivatives (430), one deuterated compound (339, D replaces H) and one

acetylated compound (434) are shown in Fig. 21 and 22. The mass

spectra of two spiro-(benzothiazoline)pyrazolones (431) as well as

their deuterated derivatives (431), D replaces H) were also recorded

(Fig. 23). Suggested fragmentation pathways of these two classes of

compounds (430) and (431) are outlined in Schemes 39 and 40. Table

5 contains the mass measurements carried out on some of the impor-

tant ions in compounds (339), (403) and (418).
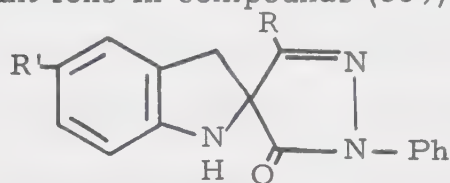
(430); general structure

(339); $R = CH_3$, $R' = H$

(343); $R = Ph$, $R' = H$

(346a); $R = CH_3$, $R' = Cl$

(346b); $R = CH_3$, $R' = OCH_3$

(346d); $R = CH_3$, $R' = OCOCH_3$
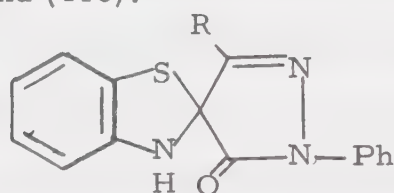
(431); general structure

(403); $R = CH_3$

(418); $R = Ph$
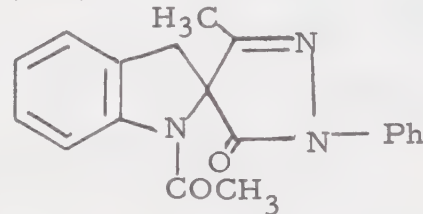
(434)

All compounds (430) displayed strong $(M-1)^+$ ions (a) due

to the loss of a hydrogen atom from the methylene group in the indoline

ring. The fact that there was little or no contribution to this loss,

from the C-methyl group in the pyrazolone ring was illustrated by the

presence of a strong $(M-1)^+$ ion (21%) in the spectrum of (343) where

no methyl substituent is present. Also, this ion was absent from the
sulfur analogs (431). Additional evidence for the origin of this proton
was found when the deuterated compound (339, D replaces H) was
examined. It lost only one mass unit to provide the $(M-1)^+$ ion.

One of these methylene protons in (430) also contributes
to the $(M-17)^+$ ion present in all the spectra of these compounds. An
accurate mass measurement of this ion in compound (339) revealed
that it was due to the loss of an OH˙ radical from the molecular ion.
Again, this ion was absent from the sulfur analogs (431). Deuterium
labelling ruled out any contribution from the amine proton, since this
ion at m/e 260 in (339) was located at m/e 261 in the deuterated
compound. There is no evidence for the structure of the $(M-OH)^+$ ion,
however, based only on the tentative mechanism illustrated in Scheme
38, it is identified as the ion (b). This $(M-17)^+$ ion was also present
in the mass spectra of some spiro-(tetrhydroquinoline)pyrazolone
derivatives (337) but not in the spiro (dihydrobenzothiazine)pyrazolones
(419).

(430), M⁺
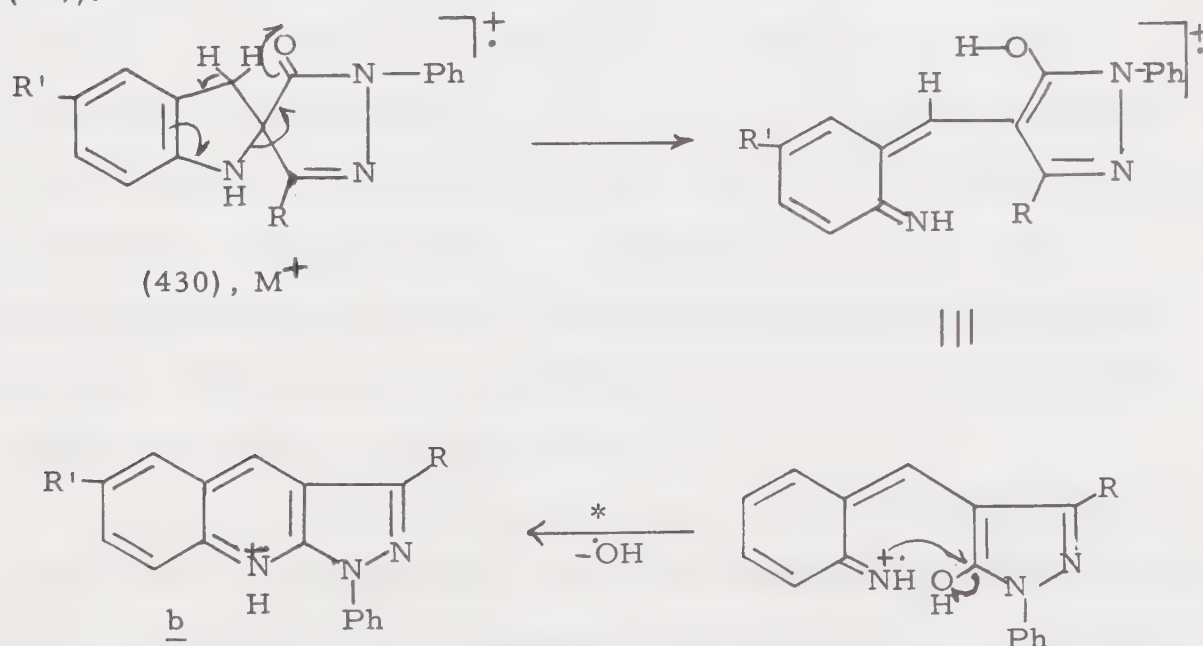
Scheme 38

Another important primary process demonstrated in the spectra of both compounds (430) and (431) was the expulsion of a carbon monoxide molecule from the molecular ions. In contrast to what was reported earlier by Maier et al (1969), the $(M-CO)^+$ ions produced here were present in appreciable intensity. The cyclic structures (c_2 in Scheme 39 and a_2 in Scheme 40), as well as open chain structures, can be suggested for this fragment. The former are in agreement with the commonly accepted cyclic structures for $(M-CO)^+$ ions in most organic compounds (Beynon et al, 1959; Bursey and Elwood, 1968).

In the spiro-indoline derivatives (430), the $(M-CO)^+$ ions fragmented further by four different pathways which gave rise to many prominent ions in the spectra (see Scheme 39). Relatively weak ions are produced by the expulsion of CH_3CN or PhCN molecules from the $(M-CO)^+$ ions. On the other hand, the loss of $PhN_2^\bullet$ radicals from the $(M-CO)^+$ ions may be accompanied by ring expansion to give the stable ion j_1. The mode of formation of a relatively strong ion k is not clear but it might arise by the loss of a hydrogen atom from j. In compounds where $R=CH_3$, another loss of a hydrogen atom together with ring expansion could account for the presence of a relatively strong ion which is represented as m. Another major pathway is the decomposition of the $(M-CO)^+$ ion in two ways to give two strong ions g and f. The former expels an HCN molecule and the latter an RCN molecule to give ions h and i respectively.

The $(M-CO)^+$ ion in the spectra of spiro(benzothiazoline) pyrazolones (431) fragmented, with some exceptions, in a similar way. Here, the ion e, (which is analogous to g in Scheme 39), can fragment

further by the expulsion of an HCN or DCN molecule or a CS molecule

to yield ions g and f respectively. The $(M-CO)^+$ ion does not expel

an RCN molecule as was demonstrated in (430).

Several examples of primary and secondary processes

where cleavage of the N—N bond occurs are demonstrated in the spectra

of both the spiro (indoline)pyrazolones (430) and the spiro-(benzo-

thiazoline)pyrazolones (431). The expulsion of a PhNCO molecule

from the molecular ions of these compounds may be accompanied or

followed by the loss of a methyl or phenyl radical; the loss of the

former gives rise to relatively abundant ions. Abundant ion (n) in the

spectra of the indoline derivatives (430) also formed either by the loss

of a PhNCO molecule from the $(M-1)^+$ ions (a) or by the expulsion of

PhNCO molecule followed by a hydrogen atom from the molecular ion.

Another initial N—N bond scission accompanied by the expulsion of a

methyl or phenyl cyanide molecule from the molecular ion is demon-

strated in the mass spectra of both the methyl and phenyl analogs of

the spirobenzothiaolines (431). In the spectra of the spiroindolines

(430), this loss did not occur directly from the molecular ion but

rather from the $(M-CO)^+$ ion.

Maier et al (1969), in a study of the mass spectra of some

pyrazolone azomethine dyes, suggested that the very minor $(M-CO)^+$

ions found in these spectra, are intermediates in the formation of all

the other major fragments. This suggestion was based on the finding

that the carbonyl moiety was absent from all the major fragment ions.

In our study, the $(M-CO)^+$ ions, which are present in appreciable

intensities in the spectra of (430) and (431) were also deduced to be a

major source of most of the fragment ions present. However, some

other ions which incorporate the carbonyl moiety were also demon-
strated. In the indoline derivatives (430), an accurate mass measure-
ment of the ion at m/e 144 (12%) showed that 50% of this ion corres-
ponds to the formulation C_9H_6NO, for which structure p is suggested
(Scheme 39). Analogous ions ranging in intensity from 8 to 14% were
also demonstrated in the spectra of (430b-e). The corresponding ion
at m/e 162 in the mass spectrum of the sulfur analog (403) was found
to be a singlet having the formulation C_9H_8NS and that ruled out the
presence of a $C=O$ group in this fragment ion. However, the ion at
m/e 254 in the spectrum of (418) was shown by accurate mass
measurement, to be solely due to the formulation $C_{14}H_{10}N_2OS$, which
indicated the presence of $C=O$ moiety in this fragment (b).

In addition to these common fragmentations, there are
several fragments peculiar to some particular compounds. In the
acetate derivatives (346d) and (434), the initial loss of a $CH_2=C=O$
molecule from the molecular ion makes a significant contribution to
the overall fragmentation pattern. The $(M-CH_2CO)^+$ fragment ion in
(434) decomposed under electron impact in a similar way to compound
(339). On the other hand, other substituents made only a minor

(346a), M^+

(434), M^+
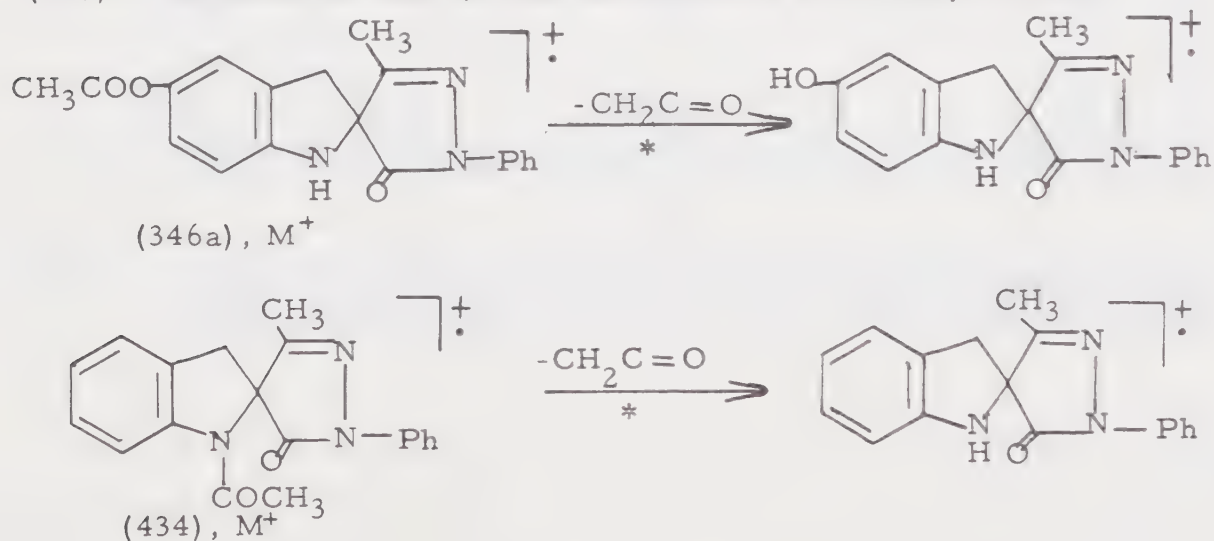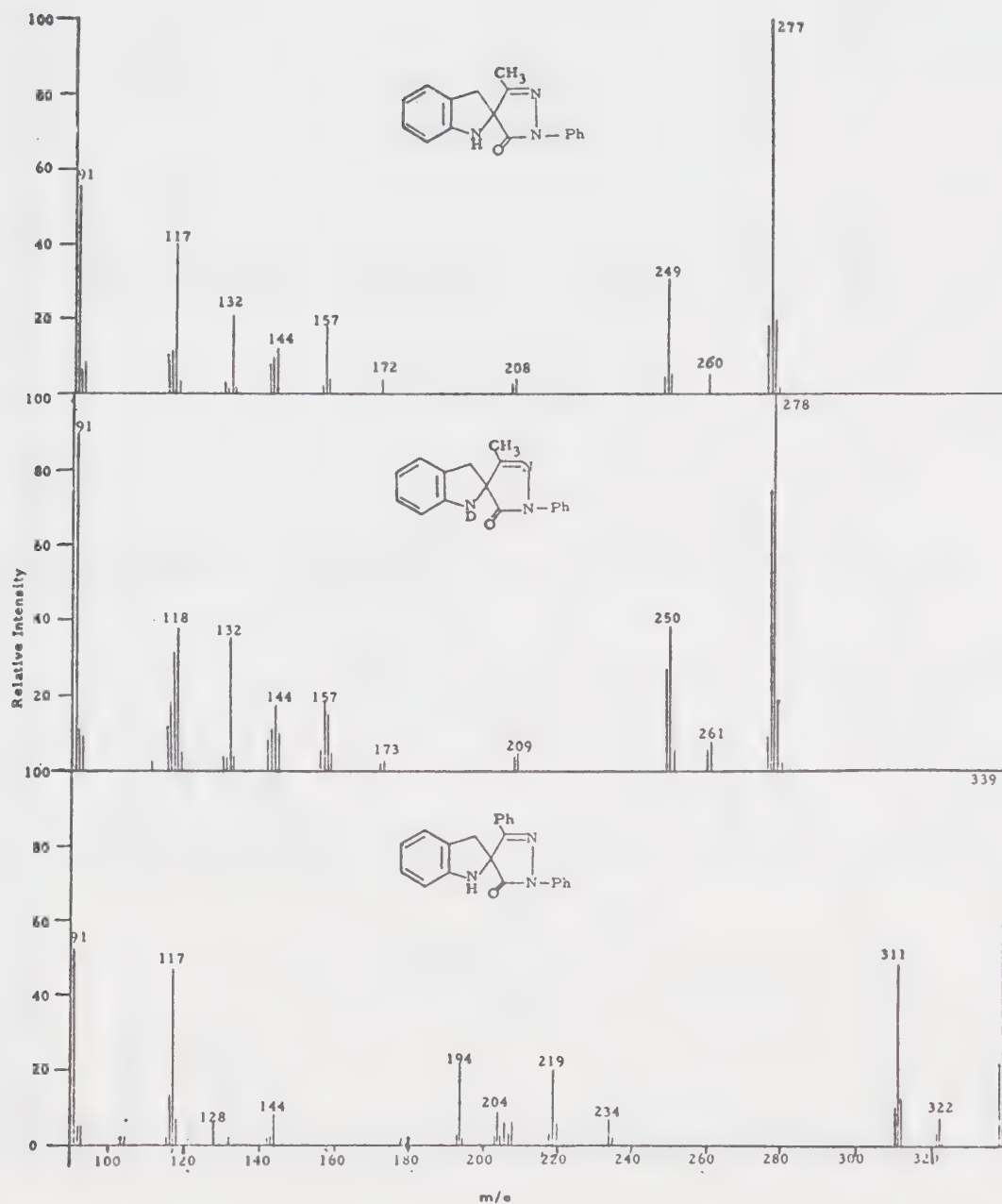
Fig. 21: Portions of the mass spectra of the spiro(indoline)pyrazolones (339), its deuterated derivative and the spiro(indoline)pyrazolone (343).
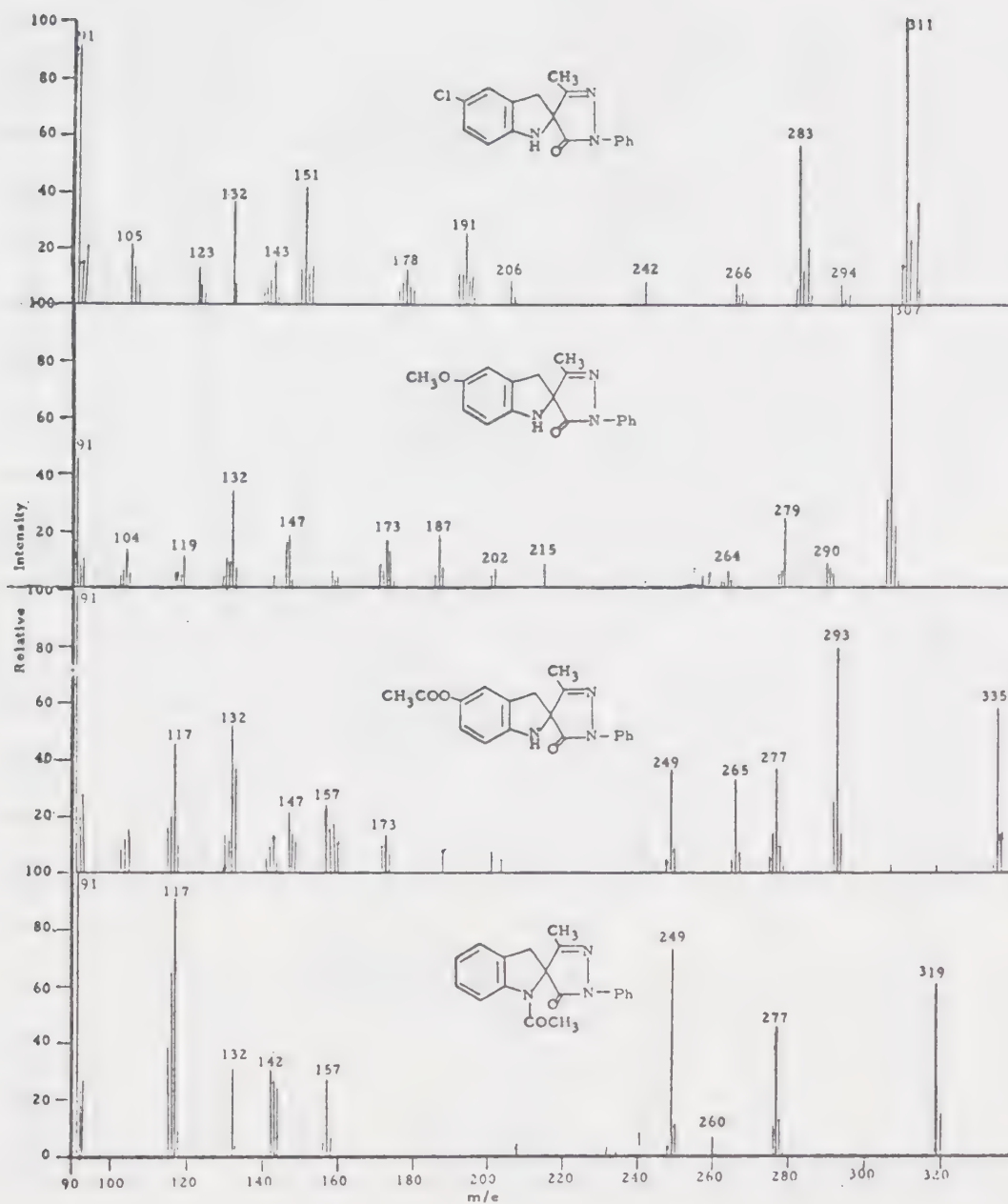
Fig. 22: Portions of the mass spectra of the spiro(indoline)-pyrazolones (346a, b, d and 434).
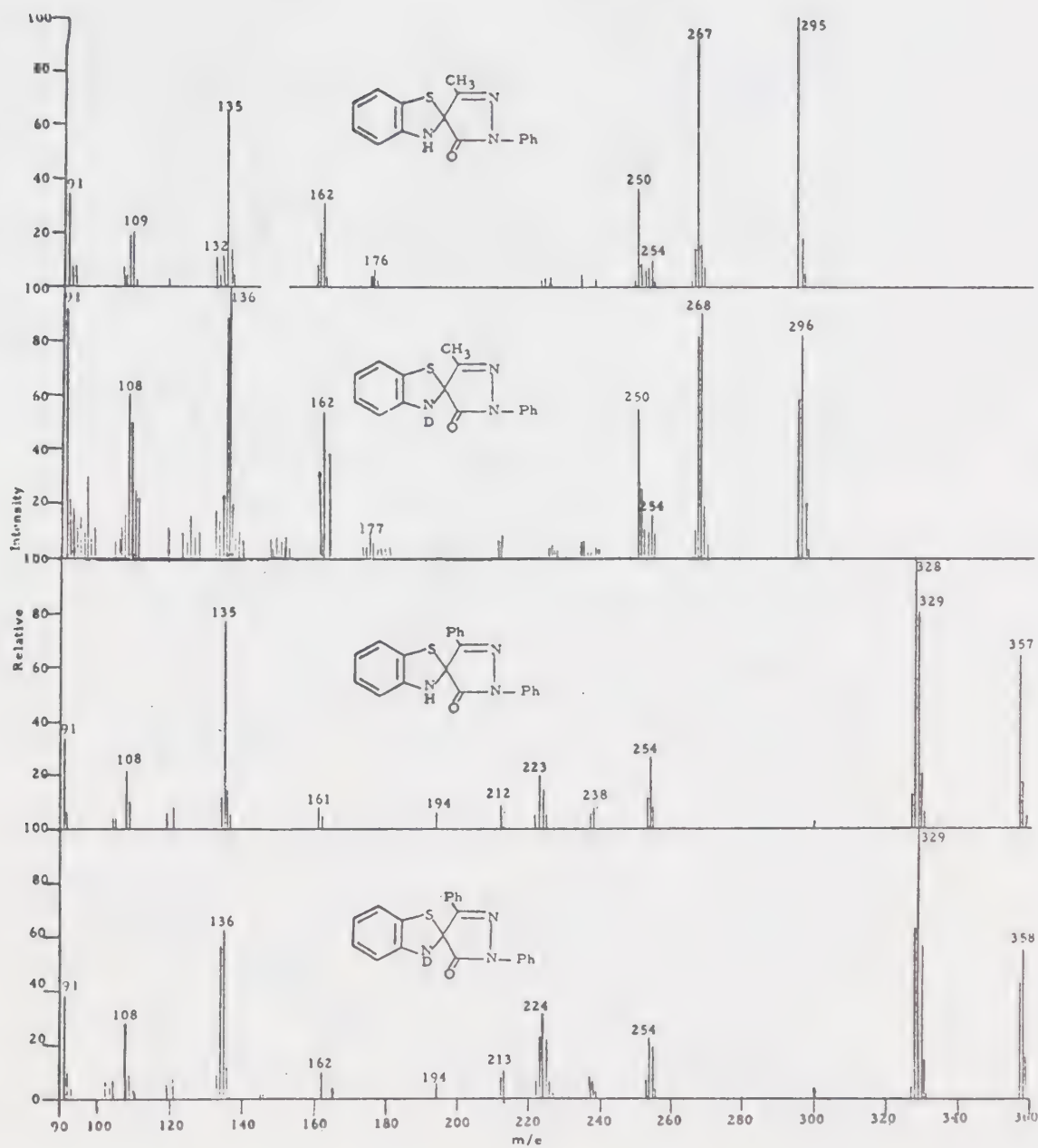
Fig. 23:   Portions of the mass spectra of the spiro(benzothiazoline)-
pyrazolones (403 and 418) and their deuterated derivatives.
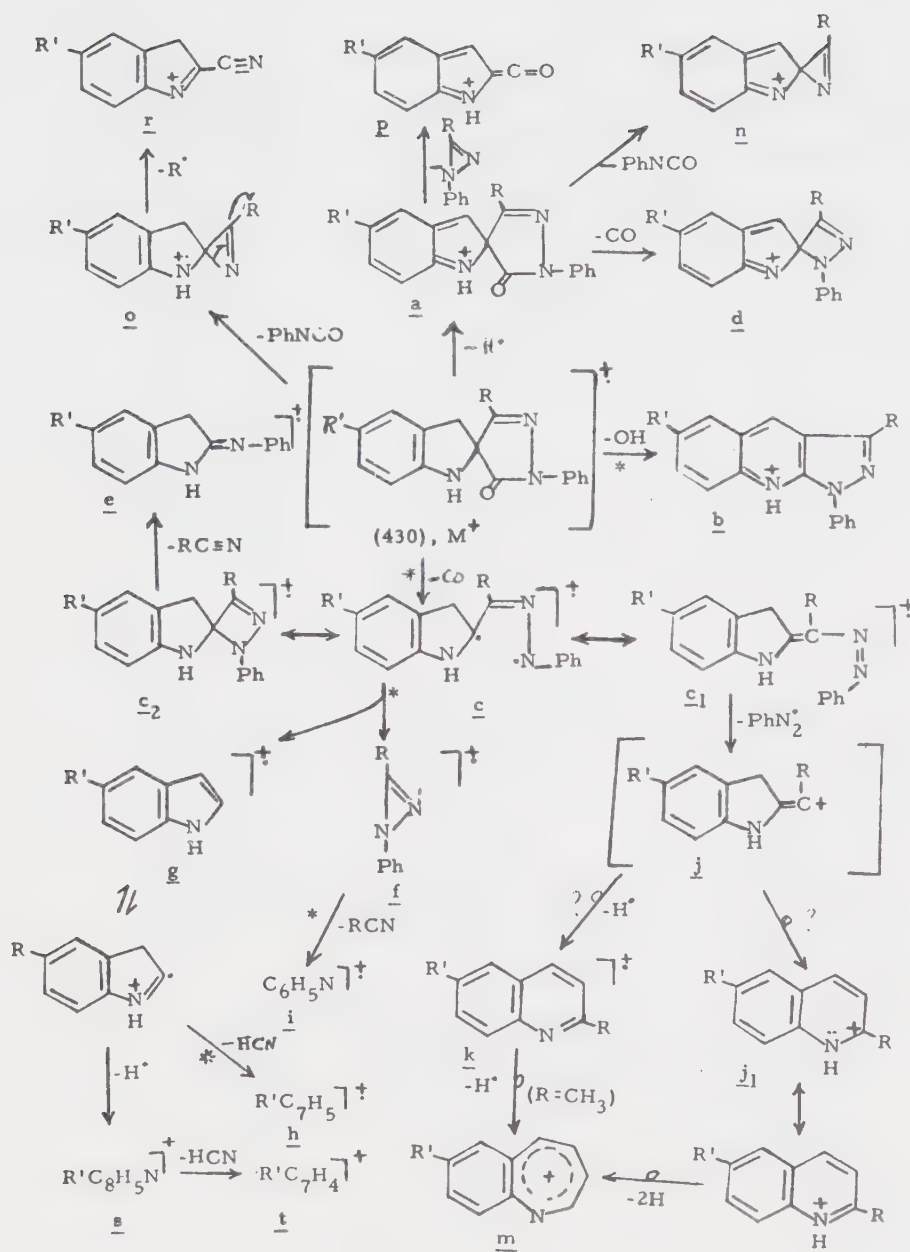
Scheme 39
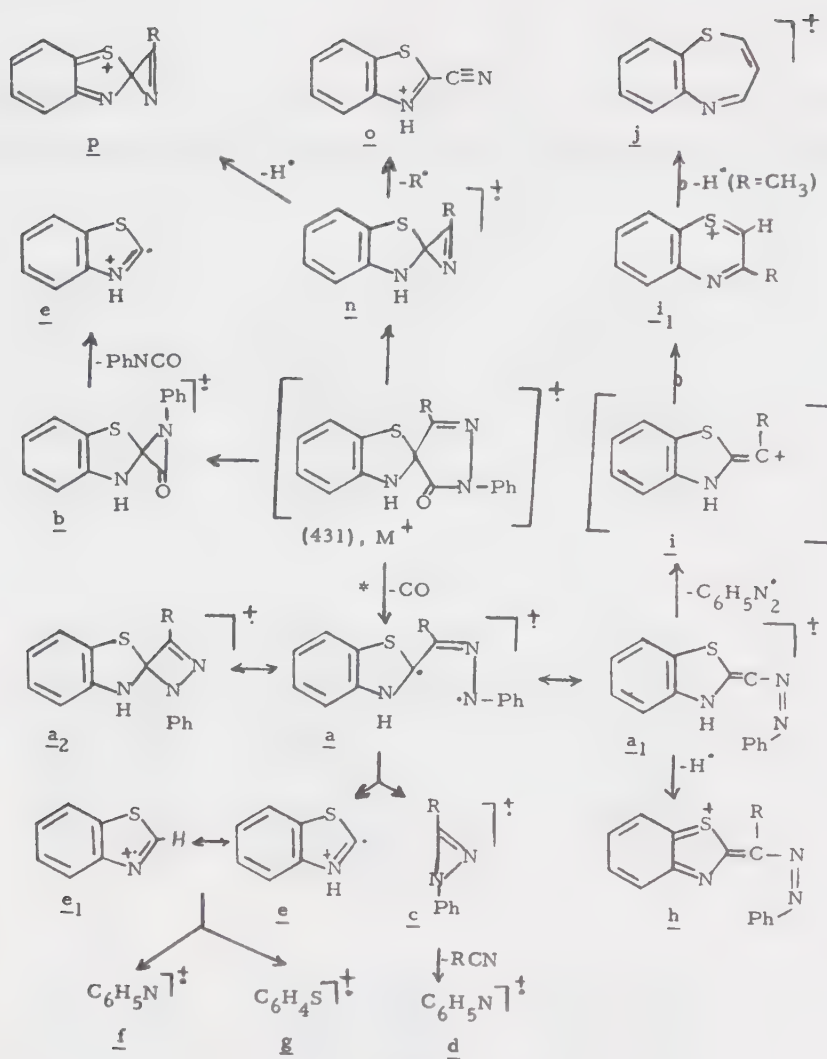
Scheme 40

Table (5). Accurate Mass Measurement Data of some of the Important Ions in the Mass Spectra of the Spiro-pyrazolones (339), (403) and (418).*

Compound	Measured m/e	Composition	Required m/e	Designation[†]
339	260.1194	$C_{17}H_{14}N_3$	260.1188	b
	249.1270	$C_{16}H_{15}N_3$	249.1266	c
	157.0769	$C_{10}H_9N_2$	157.0766	n
	144.0816	$C_{10}H_{10}N$	144.0813	j
	144.0444	C_9H_6NO	144.0449	p
	132.0688	$C_8H_8N_2$	132.0688	f
	117.0581	C_8H_7N	117.0579	g
403	295.0781	$C_{16}H_{13}N_3OS$	295.0780	M^+
	267.0831	$C_{15}H_{13}N_3S$	267.0831	a
	250.0563	$C_{15}H_{10}N_2S$	250.0565	?
	162.0377	C_9H_8NS	162.0378	i
	161.0300	C_9H_7NS	161.0300	j
	161.0177	$C_8H_5N_2S$	161.0174	o
	135.0146	C_7H_5NS	135.0143	e
418	357.0935	$C_{21}H_{15}N_3OS$	357.0936	M^+
	329.0987	$C_{20}H_{15}N_3S$	329.0987	a
	328.0907	$C_{20}H_{14}N_3S$	328.0908	h
	254.0516	$C_{14}H_{10}NOS$	254.0514	b
	135.0143	C_7H_5NS	135.0143	e

* only the important ions above m/e 117 were measured.

† as in Schemes 39 and 40.

contribution to the overall fragmentation patterns. For example, in the methoxy derivative (346b), the loss of a CH_3 radical from the molecular ion gave a weak ion (3%) at m/e 292 and the expulsion of a formaldehyde molecule (CH_2O) resulted in another ion (5%) at m/e 277.

(B) The Mass Spectra of Some Cyclic N-Hydroxy Compounds

Three spiro (N-hydroxyindoline)pyrazolones (435), two of their O-acetyl derivatives (436) and one O-methyl derivative (375) were prepared in this study and characterized by means of mass spectrometry. A literature search indicated that no detailed study
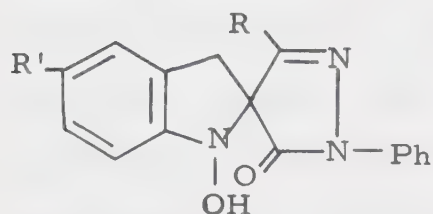
435, general structure

338; R=CH₃, R'=H

342; R=Ph, R'=H

347; R=CH₃, R'=Cl

(375)
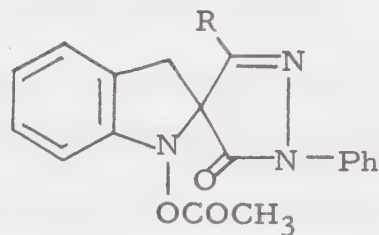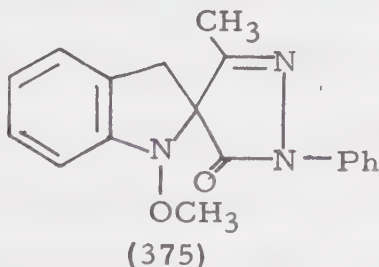
436, general structure

349; R=CH₃

361; R=Ph

of the effect of electron-impact upon cyclic N-hydroxy compounds had been reported. However, there are three isolated reports (Acheson et al, 1970; Beckett and Salami, 1972; Schweizer and Kopay, 1972) in which the presence of an (m-17)$^+$ ion in the spectrum was considered evidence of a cyclic hydroxylamine structure. To learn something of the mass spectral behavior of cyclic hydroxyl-amines and their N-acyloxy derivatives the spectra of simple refer-ence compounds were examined initially. 1-Hydroxy-2-phenyl-1,2-dihydropyridine (255), its deuterated (255, D replaces H) and

O-benzoyl (437) derivatives were prepared by reported methods (Kato

(255)

(437)
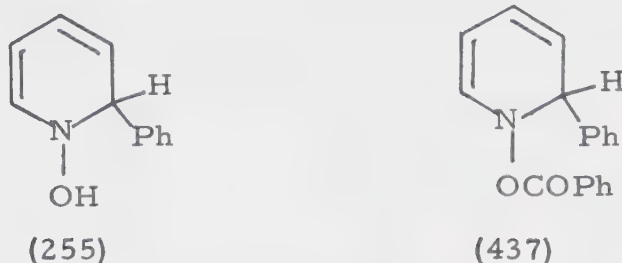
and Yamanaka, 1965; Kato et al, 1967) and their mass spectra were recorded (Fig. 24).

The molecular ion of the N-hydroxy-1,2-dihydropyridine (255) expelled an ˙OH radical to give ion of appreciable intensity at m/e 156 (Scheme 41). Also, due to the presence of a labile α-hydrogen atom in (255), a water molecule was expelled from the molecular ion giving rise to the molecular ion of 2-phenylpyridine. A weak fragment ion at m/e 157 might appear to be due to the loss of an oxygen atom, from the molecular ion of (255), but the absence of an equivalent ion at m/e 158 in the spectrum of the deuterated compound (255, D replaces H) indicated that this loss did not occur. The strongest fragment ion in the spectrum was formed by the expulsion, from the molecular ion, of the α-phenyl radical. The resulting ion at m/e 96 fragmented further by the expulsion of an ˙OH radical and a water molecule; that the former was a direct fragmentation was inferred from the presence of a metastable ion at m/e 65.01.

In addition to these fragmentations which are illustrated in Scheme 41, the mass spectrum of (255) also displaced two relatively strong fragment ions at m/e 115 and m/e 102. The former ion is believed to be formed directly from the molecular ion as shown in
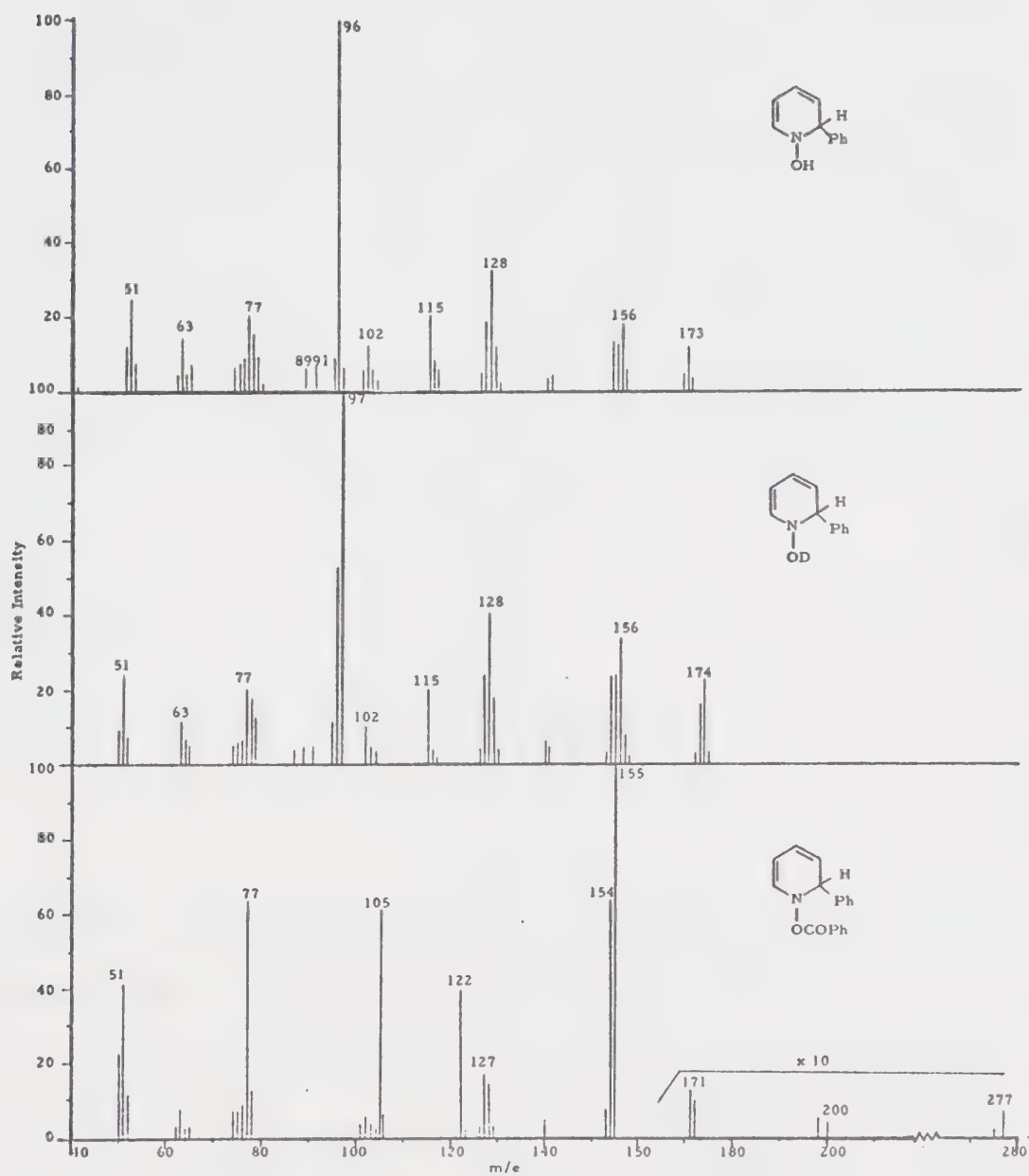
Fig. 24: Portions of the mass spectra of 1-hydroxy-2-phenyl-1,2-dihydropyridine (255), its deuterated derivative and its benzoyl derivative (437).

$C_4H_3{}^{]+}$ $\xleftarrow[*]{-C_2H_2}$ $C_6H_5{}^{]+}$

m/e 51   m/e 77

m/e 172(173)

m/e 155

$C_{11}H_8N{}^{]+}$
m/e 154

$C_{10}H_8{}^{]+}$
m/e 128

$C_{10}H_7{}^{]+}$
m/e 127

(255), M^+, m/e 173 (174)

$C_5H_4N{}^{]+}$
m/e 78

m/e 96 (97)

m/e 79

m/e 156

Scheme 41

Scheme 42; this was supported by the presence of a metastable ion at m/e 76.45. It decomposed further by the ejection of two success-ive acetylene molecules to give ions at m/e 89 and m/e 63.

(255), M^+, m/e 173

m/e 115

$C_7H_5{}^{]+}$
m/e 89

$C_5H_3{}^{]+}$ $\xleftarrow[*]{-CH\equiv CH}$
m/e 63

Scheme 42

Fragmentation of the molecular ion in the manner shown in Scheme 43
might give rise to the ion at m/e 102, but no metastable was found
to support this direct fragmentation.

$-C_3H_5NO$

$Ph - C \equiv CH$

m/e 102

(255), M^+, m/e 173
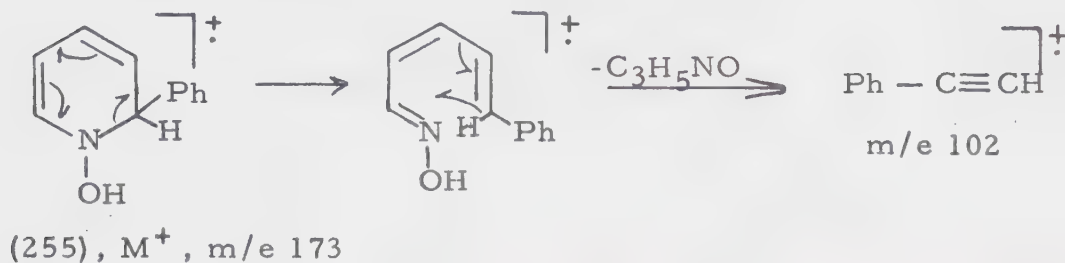
Scheme 43

In the spectrum of the N-benzoyloxy derivative (437), the
molecular ion and the fragment ion (m/e 200) resulting from the
expulsion of the α-phenyl group were of low abundance. The base
peak in (437) was formed by the ejection of a benzoic acid molecule
to give the 2-phenylpyridine ion at m/e 155. This ion fragmented
further by expelling an HCN molecule or a hydrogen atom followed
by an HCN molecule. Charge retention on the benzoyloxy function
also occurred as indicated by the strong ion at m/e 122 $(C_6H_5COOH)^+$.
In addition, the molecular ion undergoes acyl-oxygen fission with
charge retention on both the benzoyl portion and the pyridyloxy frag-
ments. The former ion fragments further in predictable fashion
(Scheme 44).

The mass spectra of the spiro-(N-hydroxy-indoline)-
pyrazolones (435), their N-acetyloxy (436) and N-methoxy (375)
derivatives are shown in Figs. 25 and 26. Although these spectra
were complex, initial fragmentation could be interpreted and were
very diagnostic and helped in the positive identification of these
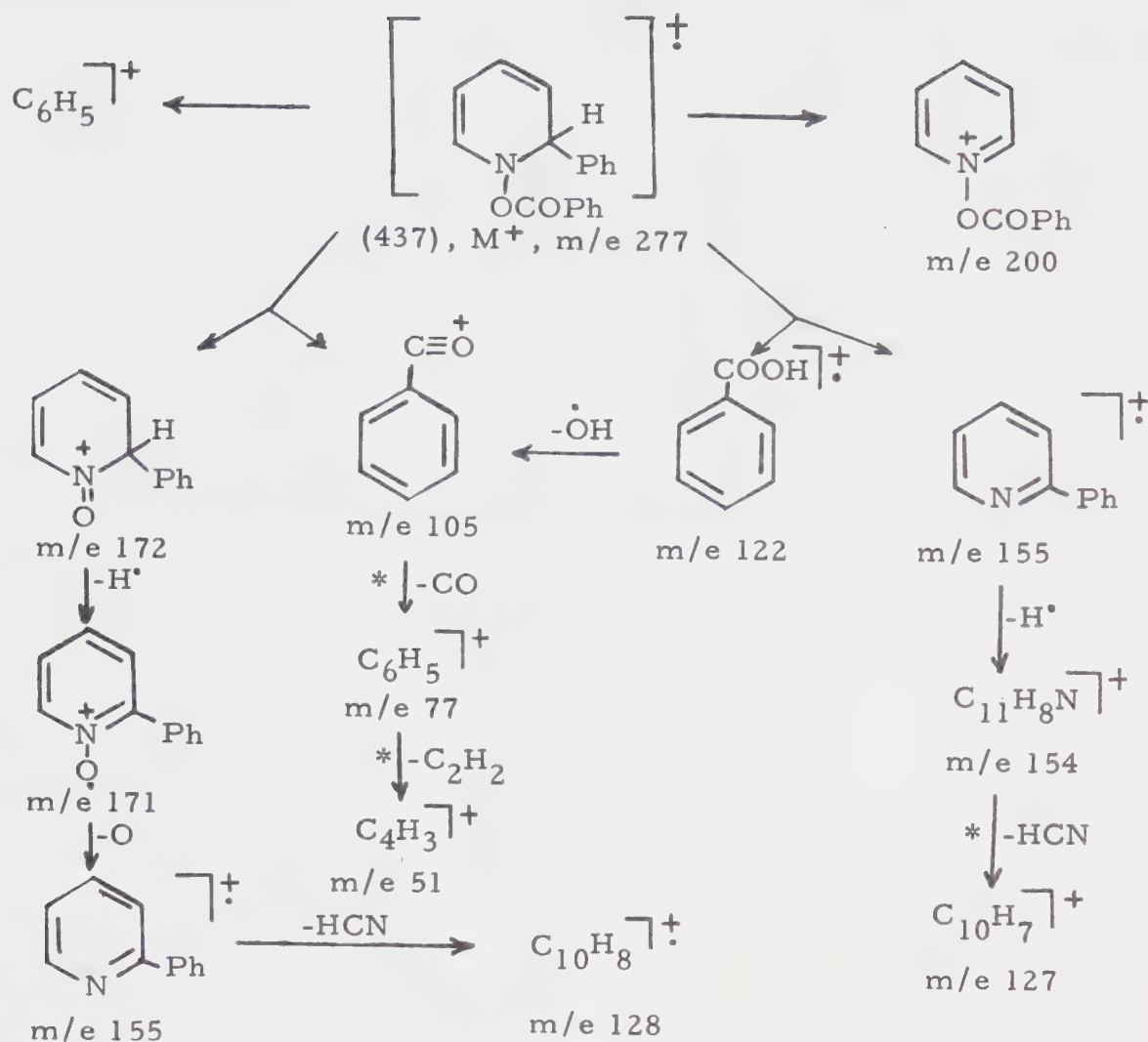
Scheme 44

compounds. The N-hydroxyindolines (435) displayed $(M)^+$ and $(M-1)^+$ ions, the abundance of which varied with the conditions in the mass spectrometer. In addition, abundant $(M-16)^+$ and $(M-17)^+$ ions were present in each of the spectra. These fragments correspond to the loss of an oxygen atom and a hydroxyl radical from the molecular ion. Strong metastables at appropriate m/e values in the spectra of (435) indicated that the transition $(M)^+ \longrightarrow (M-17)^+$ is direct. The expulsion of an oxygen atom from the molecular ions of cyclic N-hydroxy compounds has not been reported previously although Coutts
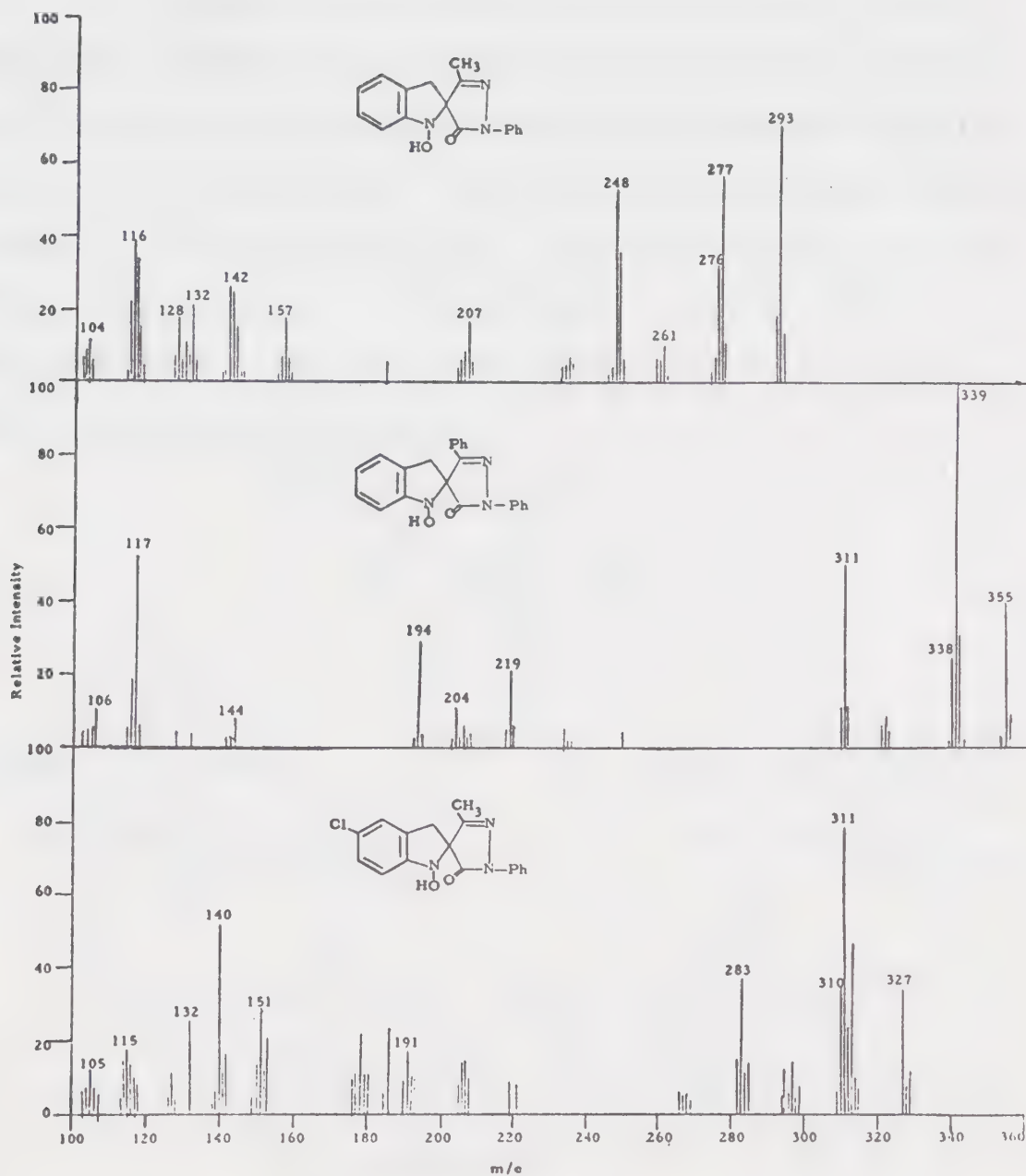
Fig. 25: Portions of the mass spectra of the spiro(N-hydroxyindoline)-pyrazolones (338, 342 and 347).

and Mukherjee (1970) have observed that aromatic hydroxylamines fragment by expelling an oxygen atom and a hydroxyl radical.

A relatively weak ion in the spectra of (435), which is identified in Scheme 45 as ion d, is due to the expulsion of a water molecule from the molecular ion; this expulsion might be direct or result from the successive losses of an oxygen atom and a hydrogen molecule. The other strong ions in the spectra of (435) are formed mainly by the expulsion of a CO molecule from the (M-OH)$^+$ ion or by fragmentation of ion c in the manner described earlier for the spiro (indoline)pyrazolones (430).
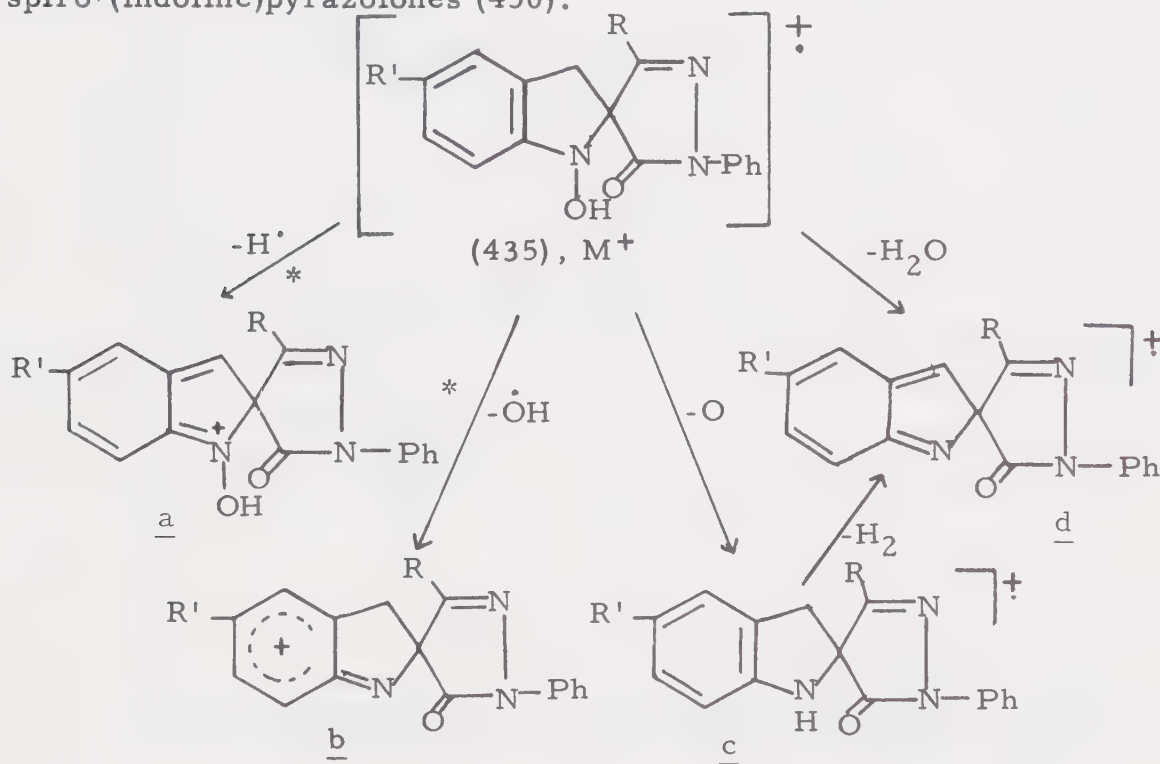
Scheme 45

Initial fragmentations of the N-acetyloxy derivatives (436) are illustrated in Scheme 46. Besides the expulsion of a ketene molecule to give ion a, each molecular ion also expelled a carbon monoxide molecule and gave the ion b. Further expulsion of a CO molecule from a or a $CH_2=C=O$ molecule from b produced a strong
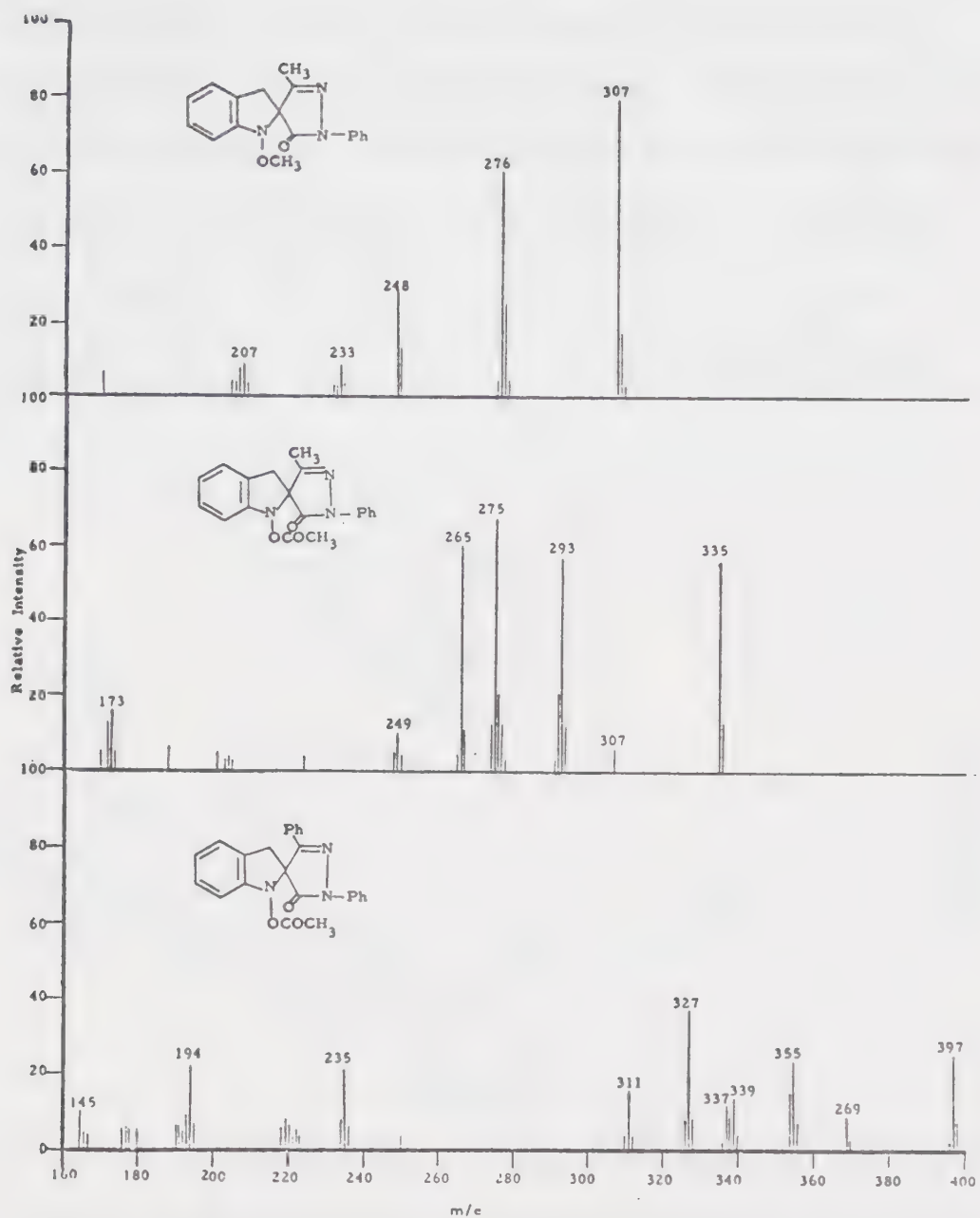
Fig. 26: Portions of the mass spectra of the spiro(N-methoxyindoline)-pyrazolone (375) and the spiro(N-acetyloxyindoline)pyrazolones (349 and 361).

ion tentatively identified as c. In addition, an $(M-59)^+$ ion and a strong $(M-60)^+$ ion are present in both spectra. These fragments might arise directly from the molecular ion by the expulsion of acetyloxy radicals and acetic acid molecules or, alternatively, by the loss of hydroxyl radicals and water molecules from the $(M-42)^+$ ions (a). No metastables to support either route were found in the spectra.

Scheme 46
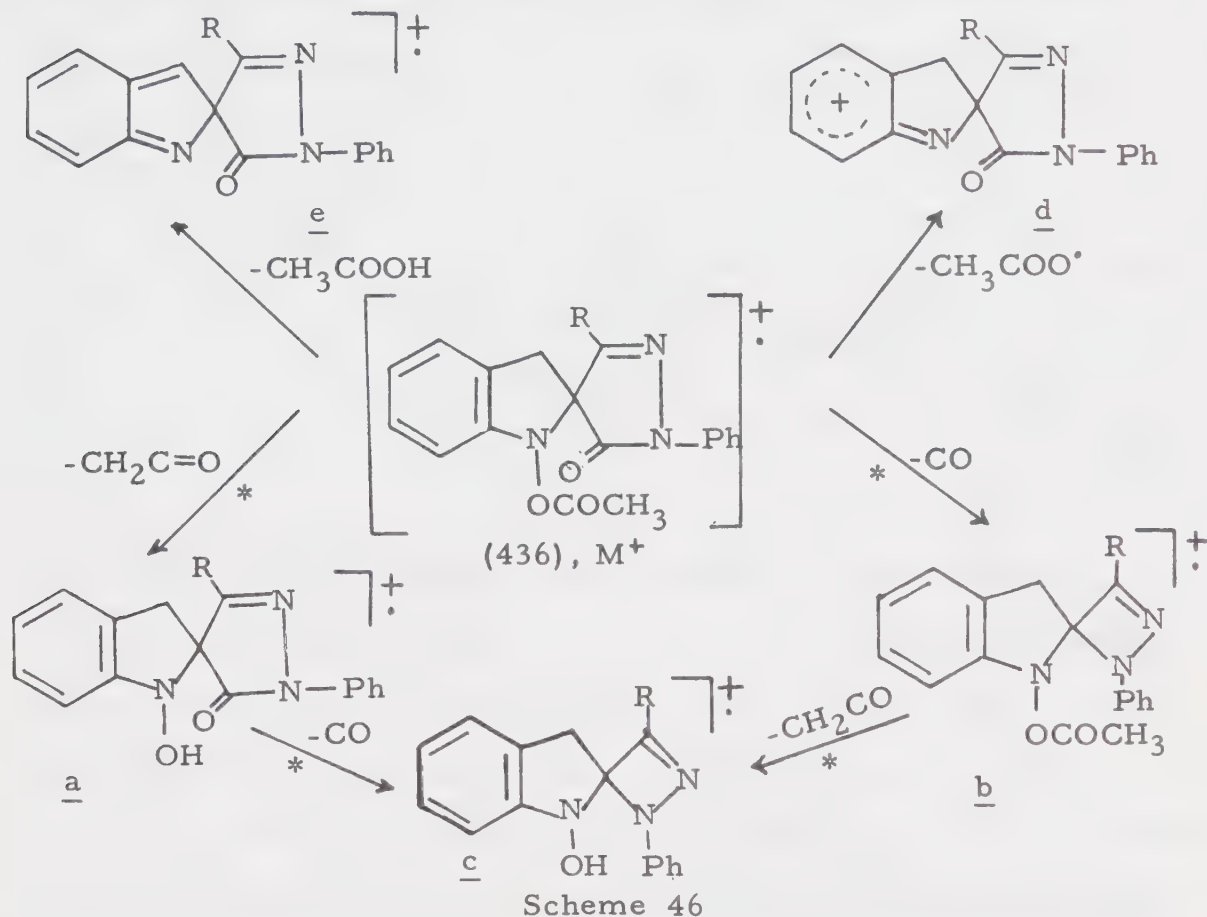
The mass spectrum of the N-methoxyindoline derivative (375) contained an abundant $(M-31)^+$ ion and a strong metastable ion at m/e 248.1 as a result of the expulsion of a methoxyl radical from the molecular ion. This is an interesting fragmentation; methyl ethers do not normally expel OCH_3 radicals except as a result of an ortho-effect displayed by some aromatic ethers (Cable et al, 1972; Coutts and Malicky, 1973). The mass spectrum of (375) also
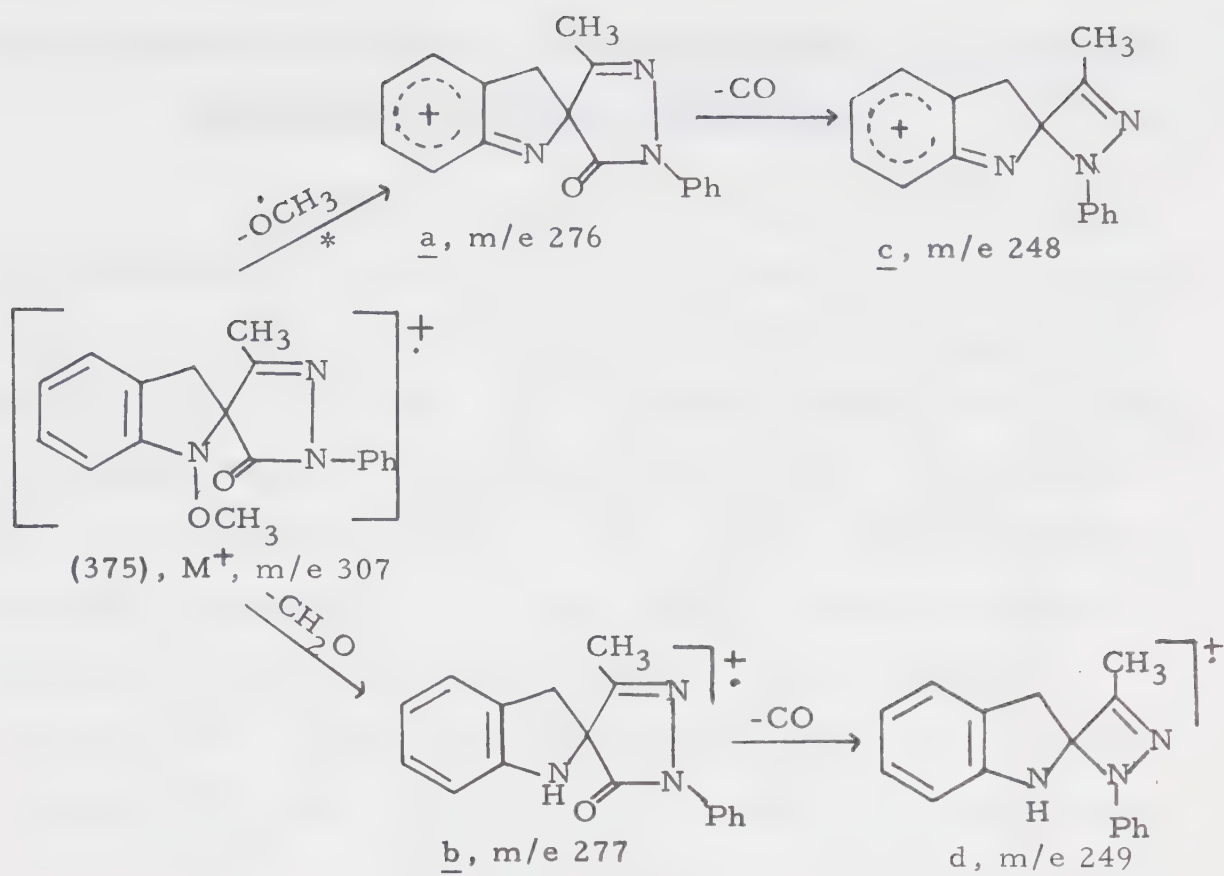
Scheme 47

contained an $(M-30)^+$ ion due to the expulsion of a formaldehyde molecule from the molecular ion (Scheme 47). The loss of a methyl radical, which generally occurs with aromatic methyl ethers, occurred with (375) only to a small extent. Both ions a and b in the spectrum of (375) fragmented further by expulsions of carbon monoxide molecules to give ions of appreciable abundance which are tentatively identified as c and d (Scheme 47).

A PRELIMINARY PHARMACOLOGICAL SCREENING OF SELECTED
COMPOUNDS PREPARED IN THIS STUDY

To complete the objectives of this study, a preliminary pharmacological screening of some selected examples of the compounds prepared was undertaken. These were the spiro(N-hydroxyindoline) pyrazolones (338) and (342), the corresponding indolines (339) and (343), the spiro(benzothiazoline)pyrazolones (403) and (418), the spiro(tetra-hydroquinoline)pyrazolones (337c,d,e,k,o,p), the spiro(dihydrobenzo-thiazine)pyrazolones (419c, e,h,j,k,l), the 4-(2-aminobenzyl)pyrazo-lones (321a,b) and their hydrochlorides, the 4-(2-aminophenylthio)-pyrazolone (416) and its hydrochloride, the 4-(2-mercaptophenylamino)-pyrazolone (406) and its dimethyl derivative (408). An observational technique similar to that described by Irwin (1962, 1964) was employed in an attempt to detect any behavioral, neurological or autonomic changes after administering each of the above compounds to mice. This random "screening" method was approached in view of the absence of guidelines to any "specific" activity to be expected from these diverse ring systems. However, because these compounds possess a 5-pyra-zolone nucleus and thus bear some chemical similarity to the known analgesics, antipyrine, aminopyrine and nifenazone, all were also evaluated for their analgesic activity. A modification of the phenyl-quinone writhing test reported by Siegmund et al (1957) was used. It should be emphasized that the limitations and inadequacies of this method are well known.

METHODS:

A) <u>For the general screening studies</u>, Alas mice of either sex, weighing 18-24 g were used.   About 12-16 hours before the experiment, the animals' diet was replaced with 20% glucose solution.   Directly before being used, they were randomly divided into groups of six mice, three were administered each of the above compounds and three were used as a control and tested concurrently.   The compounds to be tested were suspended in 1% gum tragacanth and were administered orally in a volume of 0.2 ml for each mouse.   The initial dose for all compounds was 200 mg/kg and if an effect was produced, lower doses (150, 100, 50 . . . etc. mg/kg) were used until an ineffective dose was found. After administering the test compounds, the mice were placed in separate containers for 15 minutes then transferred to an observation chamber which had six separate compartments.   A plexiglass wall allowed observation of the animals.   Following a 10-minute observation period for general behavior and orientating movements, the three mice were put together, for five minutes, in an **Anim**al Activity Cage (serial #A056, Woodard Research Corp.) which automatically recorded their movements.   This was compared with that of the control mice.   The mice were then removed from the cage and a number of neurological reflexes (e.g. righting, grasping, ... etc.) tested.   Notations were also made of animals motor activity, general appearance and behavior. At regular intervals for two hours, these tests were repeated.   The animals were then transferred to cages (three in each) and kept under observation for five days where death, if any, was recorded.

At a later stage, some of the above test compounds [the spiro(N-hydroxyindoline)pyrazolones (338) and (342), the spiro-

(indoline)pyrazolones (339) and (343) and the amine (421a)] were administered intraperitoneally to the mice at different dose levels and the animal's gross behavior was observed. Standard drugs were also given to some groups of mice when comparisons were required.

B) For the analgesic studies, female Alas mice, 17-23 g in weight were brought to this laboratory about 7 days before being used and kept on a standard diet. About 12 hours before the experiment, the food was replaced with 20% glucose solution. The animals were divided at random into groups of five mice then each group was dosed orally with one of the test substances (prepared as suspensions in 10% polysorbate 80 U.S.P. and given at initial dose of 200 mg/kg, in a volume not exceeding 0.1 ml/10 g of body weight). Twenty-five minutes later, each mouse was injected intraperitoneally with 0.25 ml of 0.02% phenyl-quinone(2-phenyl-1,4-benzoquinone, Eastman Organic Chemicals) in 5% alcohol (this solution was prepared daily and kept in amber bottle at 37° to prevent its deterioration). The mice were then placed in observation boxes and the number of writhes occurring in a 10-minute period, starting five minutes after injection, were counted for the group of five mice.

A number of control experiments were performed every day the experiment was done. These data were pooled and an average control level determined. A standard drug, aminopyrine, was administered orally in four dose levels (200, 150, 100, 50 mg/kg) to groups of five mice each then these mice were challenged with phenylquinone 25 minutes later.

The percent protection afforded by each substance was determined for each experimental group of five mice as follows:

$$\% \text{ protection} = 100 - \left(\frac{\text{experimental}}{\text{control}} \times 100 \right) \quad \text{(Hendershot and Forsaith,}$$

1959).

RESULTS:

A) The general screening studies showed that up to an oral dose of 200 mg/kg, most of the above compounds demonstrated only a weakly sedative effect in mice. Included are the spiro N-hydroxyindoline (338) and (342) which showed at this dose level some decrease in motor activity and degree of alertness. Giving this dose intraperitoneally led to no increase in these effects. On the other hand, the spiro indolines (339) and (343) demonstrated some neuroleptic properties which significantly increased when these compounds were given intraperitoneally. At an oral dose of 100 mg/kg and over, compound (339) caused a marked decrease in motor activity, reactivity and alertness, and some muscle relaxation. These symptoms were comparable to those obtained when the same compound was given intraperitoneally to mice in a dose of 50 mg/kg. Below an oral dose of 100 mg/kg or an i.p. dose of 50 mg /kg, no effects were seen. Similar signs were obtained when chlor- diazepoxide was administered i.p. in a dose of 50 mg/kg except in this case, ptosis and more muscle relaxation were observed.

The 4-(2-aminobenzyl)pyrazolone (321a) demonstrated, at an oral dose of 100 mg/kg and up, hypnotic properties marked by a preliminary excitation period then depression and sleep. A similar effect was observed when sodium pentobarbital was administered orally to mice in a dose of 50 mg/kg. The mice given compound (321a) recovered after 1-2 hours while those given the barbiturate derivative took 3-4 hours to recover. The hypnotic effect was not demonstrated below an oral dose of 50 mg/kg and was not prolonged by giving the compound intraperitoneally.

At oral or intraperitoneal dose levels of 200 mg/kg and below, none of the compounds tested produced any gross toxicity.

B) Of all the compounds tested, only the spiroindolines (339) and (343) showed weak analgesic activity when administered orally to the test mice. A decrease in the total number of writhes as compared with the controls was observed at oral doses of 200 and 100 mg/kg for (339) and 200 mg/kg for (343), but no effect was noted below this dose level. The percent protection was small, 48% and 34% for the two dose levels of (339) and 45% for the dose level of (343) as compared with 94% and 59% protection given by oral doses of 200 and 100 mg/kg of aminopyrine. Since the effects observed for the test compounds were weak, no attempts were made to administer other dose levels in order to calculate their ED_{50}.

From the results obtained, it is evident that these compounds have relatively weak neuroleptic properties. These weak properties may be due in part to the low solubility of these compounds in water.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus. All melting points quoted are uncorrected. Infrared (i.r.) spectra were recorded on a Beckman IR-10 spectrophotometer; nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian A-60 spectrometer and chemical shifts are recorded in ppm (δ) down field from tetramethylsilane (TMS). Mass spectra were determined by Dr. A. M. Hogg and his associates, Department of Chemistry, University of Alberta, with an AEI MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct Probe technique. Elemental analyses were performed by the microanalytical laboratories of the Faculty of Pharmacy and Pharmaceutical Sciences and the Department of Chemistry, University of Alberta.

The following abbreviations will be used throughout this section:

br ≡ broad

d = doublet

m = multiplet

q = quartet

s = singlet

t = triplet

I.   REDUCTIONS OF 4-(2-NITROBENZYLIDENE)-2-PYRAZOLINE-5-ONES

1,3-Diphenyl-2-pyrazolin-5-one (317b)

This compound was prepared following the procedure reported by Hinton and Mann (1959).   Phenylhydrazine (11.9 g) was slowly added to ethyl benzoylacetate (21.4 g) and the mixture warmed on a water bath for five minutes.   This solution was then poured into ether (75 ml) and stirred for two hours.   The title compound, which precipitated slowly during this time, and was collected and recrystallized from ethanol to yield an off-white solid (19.3 g), m.p. 135-7°. Reported (Hinton and Mann, 1959) m.p. 135-8°.

3-Methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a) (Coutts and Edwards, 1966).

A mixture of o-nitrobenzaldehyde (6.7 g), 3-methyl-1-phenyl-2-pyrazolin-5-one (7.0 g), fused sodium acetate (3.8 g), and acetic anhydride (12 ml) was heated on a water-bath until a homogenous red solution formed.   When cooled, a dark-red crystalline product was formed.   This was washed with water then with cold ethanol and recrystallized from ethanol to give the title compound (8.2 g) as orange-red crystals, m.p. 162-3°.   Reported m.p. 162° (Narang et al, 1934), 160-2° (Coutts and Edwards, 1966).

I.r. spectrum (nujol): 1688 (C=O); 1522 and 1337 (NO$_2$) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.35 (3H, s, CH$_3$); 7.0-8.4 (10H, m, aromatic protons).

The following compounds were prepared in a similar manner:

<u>1,3-Diphenyl-4-(2-nitrobenzylidene)-2-pyrazolin-5-one (318b)</u> was

obtained as red needles (9.9 g, m.p. 180-2°) from o-nitrobenzalde-

hyde (6.0 g) and 1,3-diphenyl-2-pyrazolin-5-one (10.0 g). Reported

(Coutts and Edwards, 1966) m.p. 181-2°.

I.r. spectrum (nujol): 1695 (C=O); 1540 and 1330 (NO$_2$) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ6.9-8.4 (15H, m, aromatic protons).

<u>4-(5-Chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one</u>

<u>(318c)</u> was obtained as orange-red needles (5.1 g, m.p. 141-2°) from

3-chloro-6 nitrobenzaldehyde (7.4 g) and 3-methyl-1-phenyl-2-pyrazolin-

5-one (7.0 g). Reported (Coutts and Edwards, 1966) m.p. 140-2°.

I.r. spectrum (nujol): 1695 (C=O); 1520 and 1333 (NO$_2$) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.35 (3H, s, CH$_3$); 7.0-8.6 (9H, m,

aromatic protons).

General Procedure for sodium borohydride and palladium-charcoal reductions.

A solution of sodium borohydride (0.5 g) in water (10 ml)

was carefully added to a suspension of palladium-charcoal (0.05 g) in

water (5 ml). The nitro compound (1.0 g), dissolved in a suitable

solvent, was added dropwise over a period of thirty minutes. Nitrogen

was bubbled through the reaction mixture during the addition of the

nitro compound and for a further fifteen minutes. The mixture was

then filtered and the filtrate acidified and diluted with ice-cold water.

The precipitated product was either filtered off or extracted into ether.

Reductions of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a).

<u>Method A:</u> Reduction with sodium borohydride in dioxane

The title compound (4.0 g) in dioxane (80 ml) was added

dropwise to a stirred solution of sodium borohydride (2.0 g) in 50%
aqueous dioxane (20.0 ml). After addition was completed, stirring
was continued for one hour. The reaction mixture was cooled and
acidified with dilute hydrochloric acid then diluted with water. The
precipitate was collected and crystallized from ethanol to give a yellow
crystalline compound (3.4 g) m.p. 168-9° which was identified as
3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one (319a).

I.r. spectrum (nujol): 2300-3200 v. br. (OH); 1605 (C=N); 1530 and
    1335 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ 2.05 (3H, s, CH_3); 3.95 (2H, s, CH_2);
    7.4 (1H, br., exchanged with D_2O, OH); 7.1-8.1 (9H, m, aromatic
    protons).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.88; N, 13.58.

                    Found: C, 65.91; H, 5.00; N, 13.39.

Method B: Reduction with sodium borohydride and palladium-charcoal
in dioxane:

        (i) Using the general procedure (p. 245), a solution of
3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (318a)
(3.0 g) in dioxane (50 ml) was reduced with sodium borohydride and
palladium-charcoal. When the filtered reaction mixture was acidified
with dilute hydrochloric acid then flooded with water (300 ml), it yielded
a dark yellow precipitate (2.8 g). Attempts to purify the crude product
by crystallization proved difficult. Chromatography on a silica gel
column using chloroform/ether (9:1) followed by evaporation of eluate
gave a yellowish crystalline compound (1.2 g), m.p. 187-8° d. (ethanol)
which was identified as spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-
phenyl-1H-pyrazolin-5'-one)] (338). This compound reduced Tollen's

reagent and gave, in the presence of alkali, a purple-red color with triphenyltetrazolium chloride.

I.r. spectrum (nujol): 1690 (C=O); 3275, br. (N—OH) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ1.97 (3H, s, CH$_3$); 3.28 (2H, br, CH$_2$); 9.67 (1H, br, exchanged with D$_2$O, N—OH); 6.7-8.1 (9H, m, aromatic protons).

N.m.r. spectrum (pyridine): δ2.1 (3H, s, CH$_3$); 3.44 (2H, doublet of doublets, J=16 Hz, CH$_2$); 12.1 (1H, br. exchanged with D$_2$O, N—OH); 7.1-7.8 (9H, m, aromatic protons).

Mass spectrum: See Fig. 25.

Anal. Calcd. for C$_{17}$H$_{15}$N$_3$O$_2$: C, 69.61; H, 5.16; N, 14.33.

Found: C, 69.62; H, 5.07; N, 14.29.

Further elution of the column with more polar solvent yielded only small amounts of dark brown oils which were not investigated.

(ii) When the above reaction was repeated and the filtered reaction mixture was acidified with dilute acetic acid then flooded with ice-cold water (300 ml), it gave a white precipitate. Crystallization from ethanol offered a white crystalline product (1.5 g) melted at 191-2° (decomp.). Infrared and n.m.r. spectra were identical to those of the N-hydroxyindoline described above. Concentration of the mother liquor yielded a white crystalline second product (0.4 g), m.p. 152-3°. This was 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321a). Reported m.p. 141-2° (Coutts and Edwards, 1966), 142° (Narang et al, 1934) (Compound erroneously identified by these authors).

I.r. spectrum (nujol): 1628 (bonded C=O); 1604 (C≡N); broad absorption between 2100 and 3500 with maxima at 3200; and 3345 (OH and

NH$_2$) cm^{-1}.

I.r. spectrum (CHCl$_3$, 2% solution):   1712 (C=O) cm^{-1}.

I.r. spectrum (DMSO, 2% solution):   1660, average (C=O); 1603 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.1 (3H, s, CH$_3$); 3.43 (2H, s, CH$_2$); 6.3-7.9 (12H, m, aromatic protons included 3 exchanged with D$_2$O for NH$_2$ and pyrazolone proton).

N.m.r. spectrum (CDCl$_3$): δ1.19 (3H, s, CH$_3$); 3.3(2H, s, CH$_2$); 6.5-8.2 (9H, m, aromatic protons); 6.0-6.5 (3H, br., exchanged with D$_2$), NH$_2$ and pyrazolone proton).

Mass spectrum: See Fig. 1.

Accurate mass measurements: 186.0790, C$_{11}$H$_{10}$N$_2$O requires 186.0793; 106.0655, C$_6$H$_6$N$_2$ requires 106.0657.

Anal. Calcd. for C$_{17}$H$_{17}$N$_3$O: C, 73.09; H, 6.13; N, 15.04.

Found: C, 73.08; H, 6.08; N, 14.91.

(iii) Reduction of the nitrobenzylidene derivative (318a) with sodium borohydride and palladium-charcoal was repeated as above and the filtrate was diluted with ice-cold water before acidification. A white precipitate (1.6 g) formed and was collected and crystallized from ethanol to give the previously identified spiro(N-hydroxyindoline) pyrazolone (338), m.p. 192-3°.   The filtrate from this was then acidified with glacial acetic acid to give a white precipitate (0.5 g) which was crystallized from ethanol into a small amount (0.08 g) of white crystals identified as spiro[(indoline)-2,4'(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (339), m.p. 126-7°.

I.r. spectrum (nujol):   1725 (C=O); 3305 (NH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.09 (3H, s, CH$_3$); 3.33 (2H, doublet of

doublets, J=16.5 Hz, CH_2); 5.57 (1H, br., exchanged with D_2O,

NH); 6.56-8.1 (9H, m, aromatic protons).

Mass spectrum: See Fig. 21.

Accurate mass measurements: See Table 5.

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15.

Found: C, 73.93; H, 5.49; N, 14.94.

The mother liquor remaining after the removal of the above product was concentrated to yield a third product (0.33 g), m.p. 153-4° which was found to be the 4-(2-aminobenzyl)pyrazolone (321a). Its infrared spectrum was identical with that of an authentic sample of (321a).

Method C: Reduction with sodium borohydride and palladium-charcoal in methanol.

Following the general procedure outlined above (p. 245), a solution of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (2.0 g) in methanol (120 ml) was reduced with catalyzed (10% Pd-C) sodium borohydride. The reaction mixture was filtered and the filtrate was acidified with glacial acetic acid. A small amount (0.13 g) of a pale-yellow product, m.p. 146-9° was deposited. This was collected and recrystallized from ethanol to give a white crystalline compound, m.p. 182-3° identified (i.r. and n.m.r.) as the spiro(N-hydroxyindoline)pyrazolone (338). When the filtrate remained after collecting this product was concentrated and allowed to stand, it yielded a crystalline product (0.63 g), m.p. 151-2^O which was identical to the 4-(2-aminobenzyl) pyrazolone (321a) described above.

Reductions of 1,3-diphenyl-4-(2-nitrobenzyliden)-2-pyrazolin-5-one (318b).

Method A: Reduction with sodium borohydride in dioxane.

   The title compound (3.0 g) was reduced with sodium boro-hydride (1.5 g) as described for the reduction of the methyl analog (318a) (method A).   The resulting yellow precipitate was crystallized from ethanol as a pale-yellow solid (2.7 g), m.p. 185-6°.   This was identified as 1,3-diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (319b).

I.r. spectrum (nujol):   2400-3200 br. (OH); 1604 (C=N); 1527 and 1340 (NO$_2$) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ4.2 (2H, br. s, CH$_2$); 7.8 (1H, br. s, exchanged with D$_2$O, OH); 7.1-8.1 (14H, m, aromatic protons).

Anal. Calcd. for C$_{22}$H$_{17}$N$_3$O$_3$:   C, 71.15; H, 4.61; N, 11.31.

        Found: C, 71.30; H, 4.41; N, 11.24.

Method B: Reduction with sodium borohydride and palladium-charcoal in dioxane.

   1,3-Diphenyl-4-(2-nitrobenzylidene)-2-pyrazolin-5-one (3.0 g) was reduced according to the general procedure using dioxane (60 ml) as solvent.   The reaction mixture was filtered and the filtrate acidified with dilute acetic acid then flooded with ice-cold water (300 ml).   The precipitate formed was crystallized from ethanol into an off-white solid   (1.2 g), m.p. 178-9° (decomp.) which was identified as spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (342).   This compound reduced Tollen's reagent and gave postive tests with triphenyltetrazolium chloride.

I.r. spectrum (nujol):   1696 (C=O); 3347 (N—OH) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ3.47 (2H, br. s, CH$_2$); 9.8 (1H, br. s,

exchanged with D_2O, N-OH); 6.7-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 25.

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.79; N, 11.82.

Found: C, 74.23; H, 4.87; N, 11.89.

Concentration of the mother liquors after the removal of the above product gave 0.35 g of second compound, 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b), m.p. 151-3°. Reported (Coutts and Edwards, 1966) m.p. 109-10° (compound erroneously identified by these authors).

I.r. spectrum (nujol): 1625 (bonded C=O); 1600 (C=N); 2200-3400 broad with maxima at 3170 and 3350 (OH and NH_2) cm^{-1}.

I.r. spectrum ($CHCl_3$, 2% solution): 1711 (C=O) cm^{-1}.

I.r. spectrum (DMSO, 2% solution): 1654, average (C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ3.68 (2H, s, CH_2); 6.3-8.0 (17H, m, aromatic protons included 3 exchanged with D_2O, NH_2 and pyrazolone proton).

N.m.r. spectrum ($CDCl_3$): δ3.63 (2H, s, CH_2); 6.4-8.2 (14H, m, aromatic protons); 5.0-5.6 (3H, br., exchanged with D_2O, NH_2 and pyrazolone proton).

Mass spectrum: See Fig. 1.

Accurate mass measurements: 248.0945, $C_{16}H_{12}N_2O$ requires 248.0950; 106.0661, C_7H_8N requires 106.0657; 93.0584, C_6H_7N requires 93.0579.

Method C: Reduction with sodium borohydride and palladium-charcoal in methanol.

The title compound (2.0 g) in methanol (100 ml) was reduced as described in the general procedure (p. 245). When the

reaction mixture was acidified with glacial acetic acid, some yellow crystals (0.08 g), m.p. 176-8° separated. This was found to be the spiro(N-hydroxyindoline) pyrazolone (342). The filtrate was concentrated to half the original volume. When cooled, it yielded a pale-yellow solid which was recrystallized as off-white crystals from ethanol (0.56 g), m.p. 148-51° identified (i.r.) as 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b).

Reductions of 4-(5-chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (318c).

Method A: Reduction with sodium borohydride in dioxane.

The title compound (3.0 g) was reduced according to the method described for the reduction of the analogs (318b, c) (Method A). Crystallization of the resulting precipitate (2.65 g) from ethanol gave 4-(5-chloro-2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (319c) as a pale-yellow solid, m.p. 145-6°.

I.r. spectrum (nujol): 2100-3300 br. (OH); 1526 and 1342 (NO_2) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ 2.12 (3H, s, CH_3); 4.03 (2H, s, CH_2); 7.1-8.3 (8H, m, aromatic protons); 11.0-12.7 (1H, br. s, exchanged with D_2O, OH).

Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$: C, 59.39; H, 4.10; N, 12.22.

Found: C, 59.53; H, 4.21; N, 12.47.

Method B: Reduction with sodium borohydride and palladium charcoal in dioxane.

The title compound (2.0 g) in dioxane (50 ml) was reduced according to the general procedure (p. 245). The filtrate, on acidification with dilute acetic acid and dilution with water, yielded a white precipitate (1.3 g). Crystallization from ethanol gave spiro[(5-chloro-

1-hydroxyindoline)-2,4'(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)

(347) as a white solid, m.p. 143-5° which reduced Tollen's reagent

and gave a positive reaction with triphenyltetrazolium chloride.

I.r. spectrum (nujol): 1685 (C=O); 3280, br. (N—OH); 1605 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.2 (3H, s, CH$_3$); 3.46 (2H, s, CH$_2$);

   6.9-8.1 (8H, m, aromatic protons); 8.6 (1H, br., exchanged

   with D$_2$O, N—OH).

Mass spectrum: See Fig. 25.

Anal. Calcd. for C$_{17}$H$_{14}$ClN$_3$O$_2$: C, 62.29; H, 4.30; N, 12.82.

   Found: C, 62.13; H, 4.48; N, 13.09.

The mother liquors, on concentration gave small amounts

(0.18 g) of white crystals melted at 118-20° which was identified as

4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazoline-5-one

(321c).

I.r. spectrum (nujol): 1630 (bonded C=O); 1602 (C=N), 2100-3420,

   br. with maxima at 3230 and 3390 (OH and NH$_2$) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.08 (3H, s, CH$_3$); 3.48 (2H, s, CH$_2$);

   6.4-8.0 (11H, m, aromatic protons included 3 exchanged with

   D$_2$O).

Anal. Calcd. for C$_{17}$H$_{16}$ClN$_3$O: C, 65.06; H, 5.14; N, 13.39.

   Found: C, 65.12; H, 5.21; N, 13.45.

Method C: Reduction with sodium borohydride and palladium-charcoal
in methanol.

   The general procedure described on p. 245 was used for

the catalytic (Pd-C) sodium borohydride reduction of the title compound

(2.0 g) in methanol (120 ml). The filtered reaction mixture was acidi-

fied with glacial acetic acid then concentrated (50 ml). When cooled,

4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one
(321c) separated as pale-yellow solid (1.1 g), m.p. 110-3°.   Recry-
stallization twice from ethanol raised the m.p. to 119-20°.

Reductions of 3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one
(319a).

Method A: Reduction with sodium borohydride and palladium-charcoal
in sodium hydroxide solution.

      Following the general procedure outlined on p. 245,
a solution of the title compound (4.0 g) in 10% aqueous sodium hydroxide
(80 ml) was reduced with sodium borohydride and palladium-charcoal.
The filtered reaction mixture was acidified with ice-cold dilute acetic
acid to give a copious white precipitate.   This was crystallized from
ethanol to white needles (3.4 g), m.p. 153-4°.   The i.r. and n.m.r.
spectra of this product were identical to those of 4-(2-aminobenzyl)-3-
methyl-1-phenyl-2-pyrazolin-5-one (321a).

      When the filtrate was acidified with dilute hydrochloric
acid, it yielded a pale-yellow precipitate.   Crystallization from
methanol gave 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one
(321a) hydrochloride, m.p. 253-4°.   The same compound was obtained
quantitatively as white crystals, m.p. 255-6° when dry hydrogen chloride
was bubbled through a solution of (321a) in tetrahydrofuran.

I.r. spectrum (nujol):   1900-3280, broad with low intensity maxima at
    2080, 2630 and 3090 cm^{-1}

Anal. Calcd. for $C_{17}H_{18}ClN_3O$:   C, 64.65; H, 5.74; N, 13.31.

                    Found: C, 64.71; H, 5.72; N, 13.19.

Method B: Reduction with iron and ferrous ammonium sulfate.

Reduced iron (2.0 g) was added to a solution of the title compound (1.0 g) in ethanol (60 ml) and the mixture was heated to boiling.   An aqueous solution (25 ml) of ferrous ammonium sulfate (0.6 g) was added to the mixture and heating was continued for two hours.   The filtered reaction mixture was evaporated to dryness, and the dried residue was heated with absolute ethanol (15 ml) and filtered. The filtrate, on evaporation, yielded an off-white solid (0.62 g), m.p. 148-52°.   This was recrystallized from ethanol to give a colorless solid, m.p. 181-2°, the infrared spectrum of which indicated that it was spiro[(1-hydroxyindoline)-2,41-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (338).

When this reaction was repeated, the results were not consistent.   It sometimes gave the above compound but on other occasions it yielded the 4-(2-aminobenzyl) pyrazolone (321a) or a mixture of both products.   When a mixture was obtained, it was dissolved in 10% sodium hydroxide then extracted with ether.   Evaporation of the dried ether extract yielded the spiro (N-hydroxyindoline) pyrazolone (338).   Acidification of the aqueous layer with acetic acid gave the 4-(2-aminobenzyl)pyrazolone (321a).

Method C: Reduction with zinc and ammonium chloride.

Ammonium chloride (0.2 g) in water (10 ml) was added to a solution of 3-methyl-4-(2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (1.0 g) in dilute (50%) ethanol (40 ml).   Zinc dust (0.5 g) was added and the mixture was refluxed for two hours under nitrogen.   The filtered reaction mixture was dried under vacuum, dissolved in absolute ethanol and refiltered.   Concentration of the

filtrate yielded white crystals m.p. 125-6°. Recrystallization from ethanol raised the m.p. to 128-9°. This compound was identified (i.r. and mixed m.p.) as the spiro(indoline)pyrazolone (339) described earlier (p. 248).

Method D: Reduction with zinc and acetic acid.

Zinc dust (1.0 g) was added in small quantities to a stirred solution of the title compound (2.0 g) in boiling glacial acetic acid (20 ml). The mixture was heated under reflux for six hours then filtered and the filtrate was diluted with water (100 ml). The yellow flocculant precipitate formed was collected and crystallized from aqueous ethanol as yellow solid, m.p. 166-8° identified as 3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (376a). Reported (Brack, 1962) m.p. 178°.

I.r. spectrum (nujol):   1618 (C=N) cm^{-1}; no NH or OH bands.

N.m.r. spectrum (CDCl$_3$): δ 2.78 (3H, s, CH$_3$); 7.3-9 (10H, m, aromatic protons).

Mass spectrum: 259 (M$^+$, 100%), 258 (27%), 244 (33%), 218 (21%).

Anal. Calcd. for C$_{17}$H$_{13}$N$_3$:   N, 16.21.

Found: N, 15.38.

The same compound was obtained in low yield (0.15 g), when 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) was heated under reflux in acetic acid (10 ml) for three hours. Evaporation of acetic acid gave a yellow oil which crystallized from ethanol into dark yellow crystals, m.p. 158-61°.

Method E: Catalytic hydrogenation.

(i) A solution of 3-methyl-4-(2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (1.0 g) in absolute ethanol (150 ml) was

hydrogenated at room temperature and atmospheric pressure in the presence of a catalytic amount (~30 mg) of platinum oxide. After the uptake of hydrogen had ceased, the catalyst was removed by filtration and the solvent evaporated, leaving a solid residue (0.58 g) which was crystallized from ethanol to colorless crystals m.p. 153-4°. Infrared and n.m.r. spectra of this product were identical with those of the 4-(2-aminobenzyl)pyrazolone (321a).

(ii) The above reduction was repeated and the reaction mixture was set aside for 24 hours then filtered. Evaporation of the solvent yielded a colorless solid, the i.r. spectrum of which showed absorption bands at 1690 (C=O) and a broad band between 2100 and 3500 with maxima at 3200, 3340 and 3400 cm^{-1}. This product was treated with dilute sodium hydroxide solution and extracted with ether. The ethereal layer was washed with water, dried (Na$_2$SO$_4$) and evaporated. The solid residue formed (0.8 g) crystallized from ethanol into color-less crystals (0.32 g), m.p. 146-9° identified as spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-methyl-1',2',3',4'-tetrahydro-quinoline)] (337a).

I.r. spectrum (nujol): 1690 (C=O); 3405 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ1.06 (3H, d, J=6.5 Hz, CH$_3$); 1.93 (3H, s, CH$_3$); 3.01 (2H, doublet of doublets, J=16.5 Hz, CH$_2$); 3.7 (1H, s, CH); 3.86 (1H, br. s, exchanged with D$_2$O, NH); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: See Fig. 6.

Anal. Calcd. for C$_{19}$H$_{19}$N$_3$O: C, 74.72; H, 6.27; N, 13.76.

Found: C, 74.61; H, 6.04; N, 13.67.

Acidification of the sodium hydroxide solution with dilute

acetic acid gave a white flocculant precipitate (0.3 g) which was cry-
stallized from ethanol to yield 4-(2-aminobenzyl)-3-methyl-1-phenyl-
2-pyrazolin-5-one (321a) as a colorless solid, m.p. 151-2°.

(iii) The previous reaction was repeated in propanol
(150 ml). Crystallization of the alkali-soluble product gave 0.26g
of the 4-(2-aminobenzyl)pyrazolone (321a), m.p. 150-2°. The
ethereal extract was evaporated and crystallized from ethanol yielding
a colorless solid (0.44 g), m.p. 141-3° identified as spiro[(3-methyl-
1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydro-
quinoline)] (337b).

I.r. spectrum (nujol): 1690 (C=O), 3390 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ1.0-1.8 (5H, m, CH$_2$CH$_3$); 1.88 (3H, s,
CH$_3$); 3.05 (2H, doublet of doublets, J=16.5 Hz, CH$_2$); 3.5 (1H, s,
CH); 4.05 (1H, br. s, exchanged with D$_2$O, N H); 6.5-8.2 (9H,
m, aromatic protons).

Mass spectrum: 319 (M$^+$, 100%), 302 (2%), 290 (62%), 146 (90%).

Anal. Calcd. for C$_{20}$H$_{21}$N$_3$O: C, 75.21; H, 6.63; N, 13.16.

Found: C, 75.40; H, 6.71; N, 12.98.

(iv) When the same reduction was performed in methanol
(150 ml), it yielded a solid product which crystallized from methanol
into colorless crystals (0.28 g), m.p. 153-4°. This was identified
as spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(1',2',3',4'-
tetrahydroquinoline)] (383a).

I.r. spectrum (nujol): 1690 (C=O), 3425 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.01 (3H, s, CH$_3$); 3.0 (2H, doublet of
doublets, J=17.5 Hz, CH$_2$); 3.91 (1H, br. s, exchanged with D$_2$O,
NH); 6.6-8.3 (9H, m, aromatic protons).

Mass spectrum: See Fig. 6.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42.

Found: C, 73.87; H, 6.01; N, 13.98.

No other products was isolated from this reaction.

Reductions of 1,3-diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (319b).

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution.

The title compound (2.0 g) was reduced according to the general procedure (p.245). Acidification of the filtrate with dilute acetic acid gave a white flocculant precipitate which crystallized from ethanol into colorless crystals (1.8 g), m.p. 151-3°. This was 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b). When the filtrate was acidified with dilute hydrochloric acid, it precipitated an off-white product. Crystallization from methanol yielded 321b hydrochloride as a white solid, m.p. 211-3°. Reported (Coutts and Edwards, 1966) m.p. 182-3°.

I.r. spectrum (nujol): 1900-3200, broad with low intensity maxima at 1985, 2060, 2635 and 3080 cm^{-1}.

Anal. Calcd. for $C_{22}H_{20}ClN_3O$: C, 64.65; H, 5.74; N, 13.31.

Found: C, 64.71; H, 5.59; N, 13.26.

Method B: Reduction with iron and ferrous ammonium sulfate.

A solution of the title compound (1.0 g) in ethanol (80 ml) was reduced with reduced iron and ferrous ammonium sulfate as described for the reduction of the methyl pyrazolone (319a) (Method B). The resulting white solid (0.65 g) was crystallized from ethanol as colorless crystals, m.p. 152-3°. The i.r. spectrum of this compound was identical with that of the amine (321b) prepared as described above.

Method C: Reduction with zinc and ammonium chloride.

The title compound (1.0 g) was reduced as described for the reduction of 3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one (319a) to yield pale-yellow crystals (0.78 g), m.p. 193-4°. This was identified as spiro[(indoline)-2,4'-(1',3'-diphenyl-1$\underline{H}$-pyrazolin-5'-one)] (343).

I.r. spectrum (nujol): 1728 (C=O); 3390 (N—H) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ3.5 (2H, br. s, CH$_2$); 4.6 (1H, br. s, exchanged with D$_2$O, NH); 6.6-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 21.

Anal. Calcd. for C$_{22}$H$_{17}$N$_3$O: C, 77.85; H, 5.05; N, 12.38.

Found: C, 77.69; H, 5.14; N, 12.41.

Method D: Reduction with zinc and acetic acid.

1,3-Diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (2.0 g) was reduced with zinc dust (1.0 g) and acetic acid (20 ml) according to method D described for the reduction of the methyl analog (319a). When the reaction mixture was filtered, a dark yellow solid (0.8 g), m.p. 158-60° crystallized from the filtrate. This was collected and recrystallized from ethanol to yield golden yellow needles, m.p. 162-3°, 1,3-diphenyl-1$\underline{H}$-pyrazolo[3,4-b]quinoline (376b). A further crop (0.5 g), m.p. 157-8° was obtained from the filtrate by dilution with water (100 ml).

I.r. spectrum (nujol): 1618 (C=N) cm^{-1}; No NH or OH bands.

N.m.r. spectrum (CDCl$_3$): δ7.0-8.9 (15H, m, aromatic protons).

Mass spectrum: 321(M$^+$, 100%), 320 (30%), 244 (11%), 218 (9%).

Anal. Calcd. for C$_{22}$H$_{15}$N$_3$: C, 81.22; H, 4.71; N, 13.08.

Found: C, 81.43; H, 4.81; N, 13.41.

The same compound was obtained by heating a solution of the 4-(2-aminobenzyl)pyrazolone (321b, 0.5 g) in acetic acid (10 ml) for two hours. When the solution was cooled, the pyrazoloquinoline (376b) separated as yellow crystals (0.35 g), m.p. 158-9°.

Method E: Catalytic hydrogenation.

(i) The title compound (1.0 g) in methanol (200 ml) was hydrogenated over platinum oxide (~30 mg) at room temperature and atmospheric pressure. When the calculated amount of hydrogen was taken up, the catalyst was filtered off and the solvent evaporated to give a yellow solid. Crystallization from methanol yielded pale-yellow crystals (0.35 g), m.p. 188-9°. This was identified as spiro-[(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(1',2',3',4'-tetrahydroquinoline)] (377a)*.

I.r. spectrum (nujol): 1700 (C=O); 3365 (NH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ3.34 (2H, s, CH$_2$); 3.57 (2H, br. s, CH$_2$); 3.95 (1H, br. s, NH); 6.5-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 7.

Accurate mass measurements: 118.0653, C$_8$H$_8$N requires 118.0657.

Anal. Calcd. for C$_{23}$H$_{19}$N$_3$O: C, 78.16; H, 5.42; N, 11.89.

Found: C, 77.99; H, 5.496; N, 11.27.

The above reduction was repeated in the solvents described yielding the following compounds:

Spiro[(1,3-diphenyl-1H-pyrazolin-5-one)-4,3'-(2'-methyl-1',2',3',4'-tetrahydroquinoline] (377b) was obtained as off-white needles (0.75 g, m.p. 165-6°) when ethanol (200 ml) was used as solvent.

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* The same product was obtained when the reaction was catalyzed with palladium-charcoal.

I.r. spectrum (nujol): 1712 (C=O); 3405 (N H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ1.15 (3H, d, J=6.5 Hz, CH$_3$); 3.5 (2H, doublet of doublets, J=17 Hz, CH$_2$); 3.6 (1H, q, CH); 3.63 (1H, br. s, exchanged with D$_2$O, NH); 6.4-8.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 7.

Accurate mass measurements: 367.1680, C$_{24}$H$_{21}$N$_3$O requires 367.1685; 352.1450, C$_{23}$H$_{18}$N$_3$O requires 352.1450; 132.0813, C$_{19}$H$_{10}$N requires 132.0813.

Anal. Calcd. for C$_{24}$H$_{21}$N$_3$O: C, 78.45; H, 5.76; N, 11.43.

Found: C, 78.47; H, 5.60; N, 11.60.

Spiro[(1,3-diphenyl-1$\underline{H}$-pyrazolin-5-one)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (377c) was isolated as colorless crystals (0.59 g, m.p. 159-60°) when a solution of 1.0 g of (319b) in propanol (200 ml) was hydrogenated over platinum oxide.

I.r. spectrum (nujol): 1710 (C=O); 3415 (N-H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ0.9-1.5 (5H, m, J=6.5 Hz, CH$_2$CH$_3$); 3.35 (2H, doublet of doublets, J=17.5 Hz, CH$_2$); 3.64 (1H, br. s, exchanged with D$_2$O, NH); 6.3-8.3 (14H, m, aromatic protons).

Mass spectrum: 381 (M$^+$, 100%), 364 (2%), 352 (42%), 352 (42%), 146 (78%).

Accurate mass measurements: 381.1837, C$_{25}$H$_{23}$N$_3$O requires 381.1841; 146.0966, C$_{10}$H$_{12}$N requires 146.0970.

Anal. Calcd. for C$_{25}$H$_{23}$N$_3$O: C, 78.71; H, 6.07; N, 11.02.

Found: C, 78.63; H, 6.04; N, 11.07.

Spiro[(1,3-diphenyl-1$\underline{H}$-pyrazolin-5-one)-4,3'-(2'-phenyl-1',2',3',4'-tetrahydroquinoline)] (377d) was obtained as pale-yellow solid (0.28 g,

m.p. 207-9°) when the above reduction was repeated in benzyl alcohol (200 ml).

I.r. spectrum (nujol):   1698 (C=O);   3380 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ3.45 (2H, doublet of doublets, J=17 Hz, CH$_2$);   4.68 (1H, s, CH);   4.07 (1H br., exchanged with D$_2$O, NH);   7-7.8 (19H, m, aromatic protons).

Mass spectrum: 429 (M$^+$, 100%), 412 (2%), 352 (3%), 194 (67%), 193 (25%).

Anal. Calcd. for C$_{29}$H$_{23}$N$_3$O: C, 81.07;   H, 5.39;   N, 9.78.

Found: C, 81.12;   H, 5.43;   N, 9.80.

4-(2-Aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (321b) was isolated as colorless crystals (0.78 g, m.p. 151-2°) when a solution of 1.0 g of (319b) in dioxane (100 ml) was hydrogenated over platinum oxide.

Reductions of 4-(5-chloro-2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazo-lin-5-one (319c).

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution.

A solution of the title compound (2.0 g) in 10% aqueous hydroxide (40 ml) was reduced according to the general procedure (p. 245).   The filtrate was acidified with dilute acetic acid to give a white precipitate which crystallized from ethanol as a colorless solid (1.2 g), m.p. 119-21°.   The i.r. and n.m.r. spectra were identical with those of 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (321c).   When this compound was dissolved in aqueous sodium hydroxide, and the alkaline solution acidified with dilute hydrochloric acid, 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-

pyrazolin-5-one (321c) hydrochloride precipitated quantitatively as a pale-yellow solid, m.p. 229-30°.

I.r. spectrum(nujol): 1900-3250, broad with low intensity maxima at 2075, 2635 and 3090 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}Cl_2N_3O$: C, 58.29; H, 4.89; N, 11.99.

Found: C, 58.53; H, 5.03; N, 12.21.

Method B: Reduction with zinc and ammonium chloride.

The title compound (1.0 g) was reduced as described for the reduction of (319a) (Method C). After removal of the excess zinc and zinc oxide, the solution was evaporated. Crystallization of the dried residue from ethanol gave a white crystalline solid (0.4 g), m.p. 153-4°. This was identified as spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346a).

I.r. spectrum (nujol): 1710 (C=O); 3365 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.04 (3H, s, CH$_3$); 3.33 (2H, doublet of doublets, J=16 Hz, CH$_2$); 4.0 (1H, br. s, exchanged with D$_2$O, N—H); 6.4-8.1 (8H, m, aromatic protons).

Mass spectrum: See Fig. 22.

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48.

Found: C, 65.06; H, 4.67; N, 13.21.

Concentration of the mother liquor remaining after the removal of the above product yielded a second crystalline powder (0.15 g), m.p. 144-5° the i.r. spectrum of which was found to be identical with that of spiro[(5-chloro-1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (347).

Reactions of 4-(2-Aminobenzyl)-2-pyrazolin-5-ones (321a, b)

(1) Reactions with dimethylsulfate

   a. To an ice-cold solution of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) in 10% sodium hydroxide (15 ml), dimethylsulfate (0.25 g) was added dropwise with stirring. The mixture was heated under reflux for one hour. After cooling, the gummy precipitate formed was collected and washed with 10% sodium hydroxide then with water. Crystallization from methanol gave colorless needles (0.18 g), m.p. 191-2°. The product identified as 4-(2-aminobenzyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (324a).

I.r. spectrum (nujol): 1624 (bonded C=O); 3230 and 3375 (NH$_2$) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.2 (3H, s, C-CH$_3$); 2.98 (3H, s, N—CH$_3$); 3.35 (2H, s, CH$_2$); 5.16 (2H, br. s, exchanged with D$_2$O, NH$_2$); 6.3-7.6 (9H, m, aromatic protons).

Mass spectrum: 293 (M$^+$, 100%), 263 (61%), 56 (97%).

Anal. Calcd. for C$_{18}$H$_{19}$N$_3$O: C, 73.69; H, 6.53; N, 14.32.

       Found: C, 73.78; H, 6.43; N, 14.12.

   b. 4-(2-Aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (0.5 g) was treated with dimethyl sulfate in a similar manner to yield 4-(2-aminobenzyl)-3-methyl-1,3-diphenyl-3-pyrazolin-5-one (324b) as colorless needles (0.25 g), m.p. 195-6°.

I.r. spectrum (nujol): 1630 (bonded C=O); 3235 and 3405 (NH$_2$) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.9 (3H, s, N—CH$_3$); 3.44 (2H, s, CH$_2$); 5.17 (2H, br. s, exchanged with D$_2$O, NH$_2$); 6.3 7.9 (14H, m, aromatic protons).

Mass spectrum: 355 (M$^+$, 72%), 325 (40%), 118 (100%).

Accurate mass measurements: 325.1337, C$_{22}$H$_{17}$N$_2$O requires

325.1341, 118.0658, C_8H_8N requires 118.0657.

Anal. Calcd. for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82.

Found: C, 77.40; H, 5.97; N, 12.11.

(2) Reactions with acetic anhydride

a. A solution of 4-(2-aminobenzyl) 3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) in acetic anhydride (5.0 ml) was heated under reflux for one hour. The cooled solution was poured into 5% aqueous sodium hydroxide and stirred until homogeneous; then the alkaline solution was extracted with ether. This was dried (Na_2SO_4) and evaporated to give a yellow solid residue which crystallized from ethanol into white crystals (0.4 g), m.p. 208-9° identified as 4-(2-acetylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (332a).

I.r. spectrum (nujol): 1660 (C=O); 2500-3300 br. with maximum at 3180 (OH and NH) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ 2.14 (3H, s, CH_3); 2.20 (3H, s, CH_3); 3.57 (2H, s, CH_2); 7.0-7.9 (9H, m, aromatic protons); 9.2 (1H, br. s, exchanged with D_2O, NH).

Mass spectrum: See Fig. 2.

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08.

Found: C, 70.87; H, 5.81; N, 13.12.

b. When the above reaction was repeated and the mixture heated under reflux for three hours, a colorless crystalline product (0.43 g), m.p. 113-4° was obtained from ethanol. This was 5-acetyl-oxy-4-(2-diacetylaminobenzyl)-3-methyl-1-phenylpyrazole (326a).

I.r. spectrum (nujol): 1790 (ester C=O); 1730 and 1685 (diacetyl C=O); 1600 (C=N) cm^{-1}

N.m.r. spectrum (DMSO-d$_6$): δ 2.02 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.11 (6H, s, diacetyl protons); 3.48 (2H, s, CH_2); 7.2-7.5 (9H, m,

aromatic protons).

Mass spectrum: See Fig. 3.

Anal. Calcd. for $C_{23}H_{23}N_3O_4$: C, 68.15; H, 5.68; N, 10.37.

Found: C, 68.03; H, 5.71; N, 10.51.

This compound was insoluble in aqueous sodium hydroxide, but on stirring for several hours in 5% sodium hydroxide solution it dissolved. The solution was filtered and acidified with acetic acid to give a white precipitate which crystallized from ethanol, m.p. 208-10°. The i.r. spectrum of this product was identical with that of the mono-acetyl derivative (332a).

c. Similarly, heating 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (0.5 g) in acetic anhydride (5.0 ml) for one hour yielded 4-(2-acetylaminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (332b) as white crystals (0.41 g) m.p. 219-21° (ethanol).

I.r. spectrum (nujol): 1662 (C=O); 2100-3260 br. (NH and OH) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.1 (3H, s, CH$_3$); 3.84 (2H, s, CH$_2$); 6.8-8.0 (15H, m, aromatic protons); 9.33 (1H, br. s, exchanged with D$_2$O, NH).

Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.21; H, 5.52; N, 10.96.

Found: C, 75.22; H, 5.53; N, 10.75.

d. A triacetyl derivative, 5-acetyloxy-4-(2-diacetyl-aminobenzyl)-1,3-diphenylpyrazole (326b) was isolated as white crystals (0.4 g), m.p. 110-11° (from ethanol) when the above reaction was repeated and heating with acetic anhydride was prolonged for four hours.

I.r. spectrum (nujol): 1793 (ester C=O); 1718 and 1705 (diacetyl C=O); 1595 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.02 (6H, s, diacetyl protons); 2.2

(3H, s, OCOCH$_3$); 3.75 (2H, s, CH$_2$); 7.05-7.7 (14H, m,

aromatic protons).

Anal. Calcd. for C$_{28}$H$_{25}$N$_3$O$_4$: C, 71.93; H, 5.39; N, 8.98.

Found: C, 72.13; H, 5.18; N, 8.85.

Hydrolysis of this compound with 5% aqueous sodium

hydroxide readily gave the monoacetyl derivative (332b).

(3) Reaction with benzoyl chloride

To an ice-cold solution of 4-(2-aminobenzyl)-3-methyl-1-

phenyl-2-pyrazolin-5-one (0.5 g) in dilute sodium hydroxide (10 ml)

was added benzoyl chloride (0.75 ml) with vigorous stirring. After

one hour, more benzoyl chloride (0.5 ml) was added and stirring

continued at room temperature for a further 30 minutes. The reaction

mixture was extracted with ether then the ethereal extract was washed

successively with 10% hydrochloric acid, 10% sodium carbonate and

water. Concentration of the dried ethereal solution gave white shiny

crystals (0.51 g), m.p. 137-8° identified as 4-(2-benzoylamino)-5-

benzoyloxy-3-methyl-1-phenylpyrazole (325).

I.r. spectrum (nujol): 1760 (OCOPh); 1645 (NHCOPh); 1600 (C=N),

3315 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.12 (3H, s, CH$_3$); 3.8 (2H, s, CH$_2$);

8.0 (-H, br. s, exchanged with D$_2$O, NH); 6.8-7.9 (19H, m,

aromatic protons).

Mass spectrum: 487 (M$^+$, 4%), 382 (3%), 366 (9%), 365 (30%), 105

(100%).

Anal. Calcd. for C$_{31}$H$_{25}$N$_3$O$_3$: C, 76.37; H, 5.17; N, 8.61.

Found: C, 76.43; H, 5.33; N, 8.60.

(4)   Attempted preparation of 5-acetyloxy-4-(2-aminobenzyl)-1-phenyl-
pyrazoles (335a, b).

a.   A solution of 3-methyl 4-(2-nitrobenzyl)-1-phenyl-2-
pyrazolin-5-one (1.0 g) in acetic anhydride (10 ml) was heated under
reflux for one hour.   After cooling, the reaction mixture was poured
into ice-cold 5% sodium hydroxide solution (100 ml).   Stirring pre-
cipitated a pale-yellow solid (1.05 g) which crystallized from ethanol
yielding 5-acetyloxy-3-methyl-4-(2-nitrobenzyl)-1-phenylpyrazole
(334a) as white crystals, m.p. 85-6°.

I.r. spectrum (nujol):   1781 (C=O); 1600 (C=N) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.17 (3H, s, C−CH_3); 2.03 (3H, s,

(CO−CH_3); 4.05 (2H, s, CH_2); 7.2-8.1 (9H, m, aromatic protons).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$:   C, 64.94; H, 4.88; N, 11.95.

Found: C, 64.77; H, 5.15; N, 11.79.

b.   Acetylation of 1,3-diphenyl-4-(2-nitrobenzyl)-2-
pyrazolin-5-one (1.0 g) using the above method yielded 5-acetyloxy-1,3-
diphenyl-4-(2-nitrobenzyl)pyrazole (334b) (1.01 g) as a pale-yellow
crystalline powder, m.p. 118-9° (ethanol).

I.r. spectrum (nujol):   1790 (C=O); 1597 (C=N) cm^{-1}.

N.m.r. spectrum ($CDCl_3$): δ2.02 (3H, s, CO CH_3); 4.28 (2H, s, CH_2);

7.2-8.1 (14H, m, aromatic protons).

Mass spectrum: 413 (M^+, 12%), 371 (51%), 354 (14%), 353 (18%).

Anal. Calcd. for $C_{24}H_{19}N_3O_4$:   C, 69.70; H, 4.64; N, 10.16.

Found: C, 69.90; H, 5.06; N, 10.41.

c.   5-Acetyloxy-2-methyl-4-(2-nitrobenzyl)-1-phenyl-
pyrazole (0.5 g) in ethanol (20 ml) was hydrogenated over platinum
oxide at room temperature and atmospheric pressure.   When the

calculated amount of hydrogen was taken up, the catalyst was filtered and the solvent evaporated to yield a yellow oil. Trituration of this oil with methanol gave a pale-yellow solid (0.15 g). This was crystallized as pale-yellow crystals, m.p. 205-7°, from the same solvent and was found (i.r., mixed m.p.) to be identical to the previously identified 4-(2-acetylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (332a).

d. The above product (332a) was also obtained when a solution of 5-acetyloxy-2-methyl-4-(2-nitrobenzyl)-1-phenylpyrazole (0.5 g) in dioxane (20 ml) was reduced with sodium borohydride and palladium-charcoal. The general procedure outlined on p. 245 was followed. After acidification of the filtered reaction mixture with acetic acid, it was extracted with ether. The ethereal extract was washed with 10% sodium carbonate, dried (Na$_2$SO$_4$), and then evaporated. Crystallization of the resulting semi-solid from ethanol yielded a pale-yellow solid (0.12 g), m.p. 206-7° identified (i.r., mixed m.p.) as the 4-(2-acetylaminobenzyl)pyrazolone (332a).

e. Hydrogenation of 5-acetyloxy-1,3-diphenyl-4-(2-nitrobenzyl)pyrazole (0.5 g) over platinum oxide as described above gave a white crystalline compound (0.21 g), m.p. 218-9° (ethanol). Comparison of its i.r. and n.m.r. spectra with those of an authentic sample indicated that it was 4-(2-acetylaminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (332b).

Reactions of spiro (1-hydroxyindoline)-2,4'-(1'-phenyl-1H-pyrazolin-5'-ones)

(1) Reduction:

Method A: (i) A solution of spiro[(1-hydroxyindoline)-2,4'-(3'-

methyl-1'-phenyl-1H-pyrazolin-5'-one)] (338, 0.5 g) in ethanol (70

ml) was hydrogenated over platinum oxide with hydrogen at atmospheric

pressure and room temperature. After the theoretical amount of

hydrogen was absorbed, the catalyst was removed by filtration and the

filtrate was concentrated in vacu o, then cooled, and a white crystal-

line product (0.43 g) separated. This was recrystallized from ethanol

giving spiro[(indoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-

one)] (339) as white crystals, m.p. 129-30°.

(ii)   Spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-

pyrazolin-5'-one)] (342, 0.5 g) was hydrogenated in a similar manner

to yield the corresponding indoline (343) as a pale-yellow solid (0.38 g)

m.p. 192-4°.

(iii)   Similarly, spiro[(5-chloro-1-hydroxyindoline)-2,4'-

(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (347, 0.35 g) was reduced

by catalytic hydrogenation over platinum oxide giving the previously

identified spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-

pyrazoline-5'-one)] (346a) as colorless crystals (0.21 g), m.p. 152-3°.

Method B: (i)   To a heated solution of the spiro(N-hydroxyindoline)-

pyrazolone (338, 0.5 g) in 30 ml ethanol was added 1.0 g of reduced

iron followed by a solution of ferrous ammonium sulfate (0.3 g) in

water (25 ml) and the mixture was heated, under reflux, for ten hours

then filtered. The filtrate was evaporated to dryness and the residue

was dissolved in hot ethanol and refiltered. Cooling of this filtrate

yielded the spiro(indoline)pyrazolone (339) as white crystals (0.44 g),

m.p. 128-9°.

(ii)   Reduction of spiro[(1-hydroxyindoline)-2,4'-(1',3'-

diphenyl-1H-pyrazolin-5'-one)] (0.4 g) as described above yielded

pale yellow crystals (0.29 g) m.p. 192-4° which was identified (i.r.) as spiro[(indoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (343).

Method C: Ammonium chloride (0.1 g) in water (5 ml) was added to a stirred solution of spiro (1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one) (0.5 g) in 60% ethanol (25 ml).   Zinc powder (0.5 g) was added in small portions and the mixture was refluxed for an hour.   After removal of the excess zinc and zinc oxide, the solution was concentrated in vacuo and extracted with chloroform (50 ml).   Evaporation of the dried (CaCl$_2$) chloroform gave a white solid (0.41 g) which crystallized from ethanol as colorless crystals, m.p. 127-9° identified (i.r.) as the spiro(indoline)pyrazolone (339).

(2) Oxidation:

A)   Air was bubbled into a solution of the spiro(N-hydroxy-indoline)pyrazolone (338, 0.3 g) in 60% ethanol (15 ml) at room temperature for two hours.   After being allowed to stand overnight, the solution was evaporated and starting material was recovered. Similar results were obtained when the reaction was repeated in tetra-hydrofuran.

B)   Air was bubbled for three hours through a solution of the spiro(1-hydroxyindoline)pyrazolone (338, 0.3 g) in aqueous (60%) ethanol (25 ml) containing ammonia (1 ml) and copper sulfate (5 mg). Water (50 ml) was added and the dark-brown precipitate which formed was extracted into chloroform (20 ml).   The dried (CaCl$_2$) chloroform solution was concentrated in vacuo and the residue was crystallized from aqueous ethanol as a dark-brown solid (0.18 g), m.p. 121-4°. No satisfactory analysis could be obtained for this product, but its mass spectrum had a strong molecular ion at m/e 291 (C$_{17}$H$_{13}$N$_3$O$_3$).

This compound was tentatively identified as spiro[(2H-indolenine 1-oxide)-2,4'-(3'-methyl-1'-phenyl-2'-pyrazolin-5'-one)].

I.r. spectrum (nujol): 1728 (C=O) cm^{-1}, no NH or OH absorption.

N.m.r. spectrum (CDCl$_3$): δ2.07 (3H, s, CH$_3$); 6.7-8.2 (10H, m, aromatic protons).

(3) Attempted dehydration:

a) Concentrated sulfuric acid (0.5 ml) was added dropwise to a suspension of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) in methanol (15 ml). The mixture was heated under reflux for two hours, then left overnight at room temperature. The solution was made alkaline with dilute sodium hydroxide then reacidified with glacial acetic acid and extracted with chloroform. The dried (MgSO$_4$) chloroform solution was evaporated to dryness to give a dark-brown oil. When triturated with methanol, this oil gave a dark-yellow solid which was crystallized from the same solvent into brown crystals (0.29 g), m.p. 170-2°.

I.r. spectrum (nujol): 1635 (C=O); 3305 (NH or OH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.62 (3H, s, CH$_3$); 3.89 (3H, s, OCH$_3$); 6.8-7.7 (6 or 7H, m, aromatic protons); 9.4 (1H, br. s, exchanged with D$_2$O, NH or OH?).

Mass spectrum: 189 (M$^+$, 100%), 174 (92%), 146 (39%), 131 (9%), 119 (16%), 43 (16%).

Anal. Found (Average): C, 68.76; H, 5.31; N, 8.20.

This compound was not identified.

b) When the above reaction was repeated at 0°, it gave a dark-green oil which solidified when triturated with methanol. This was crystallized from ethanol as white crystals (0.37 g), m.p. 135-7°

identified as spiro[(5-methoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346b).

I.r. spectrum (nujol): 1710 (C=O); 3310 (N—H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.03 (3H, s, C—CH$_3$); 3.77 (3H, s, O—CH$_3$); 3.33 (2H, doublet of doublets, J=16.5 Hz, CH$_2$); 4.28 (1H, br. s, exchanged with D$_2$O, NH); 6.5-8.4 (8H, m, aromatic protons).

Mass spectrum: See Fig. 22.

Anal. Calcd. for C$_{18}$H$_{17}$N$_3$O$_2$: C, 70.34; H, 5.58; N, 13.67.

Found: C, 70.21; H, 5.49; N, 13.70.

c) Spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) was dissolved in an ice-cold mixture of dioxane (8 ml) and water (7 ml). Concentrated sulfuric acid (0.5 ml) was added dropwise and the reaction mixture was allowed to stand at room temperature for 12 hours. Dilute sodium hydroxide (10 ml) was added, and the solution was reacidified with glacial acetic acid and extracted with chloroform. Evaporation of the dried chloroform extract yielded a pale-brown solid which crystallized from aqueous ethanol into an off-white solid (0.19 g), m.p. 114-16°. Recrystallization of this alkali-soluble product from ethanol did not raise its melting point. This compound was identified as spiro[(5-hydroxy-indoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346c).

I.r. spectrum (nujol): 3100-3500 br. (NH and OH); 1709 (C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.1 (3H, s, CH$_3$); 3.29 (2H, br. s, CH$_2$); 4.7 (1H, br. s, exchanged with D$_2$O, NH); 11.1 (1H, br. s, exchanged with D$_2$O, OH); 6.7-8.3 (8H, m, aromatic protons).

Mass spectrum: 293 (M$^+$, 19%), 265 (26%).

This compound analyzed indifferently for $C_{17}H_{15}N_3O_2$.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$:   C, 69.61;   H, 5.16.

Found: C, 70.99;   H, 4.53.

(4) Reactions with nucleophiles:

a.   Reaction with hydrogen chloride

A stream of hydrogen chloride was passed through a solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) in tetrahydrofuran (10 ml) for 30 seconds at $0°$.   The solution was left standing at $0°$ for 12 hours then evaporated in vacuo to dryness.   The resulting black semi-solid was chromato-graphed on a silica gel column using petroleum ether (30-60°, 100 ml) then benzene (100 ml) as solvent.   Evaporation of the benzene eluate gave a dark-yellow solid which crystallized from ethanol yielding spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one] (346a) as white crystals (0.26 g), m.p. 153-4°.

b.   Reaction with acetic acid

A solution of the spiro(1-hydroxyindoline)pyrazolone (338, 0.5 g) in glacial acetic acid (10 ml) was heated under reflux for one hour.   The resulting red solution was added to cold water (100 ml) and the buff precipitate formed was extracted with ether.   The ethereal extract was washed with a saturated solution of sodium bicarbonate then with water and dried (Na_2SO_4).   Evaporation of this extract yielded a pale-yellow solid (0.38 g) which crystallized from ethanol into off-white crystals, m.p. 120-1°.   This was spiro[(5-acetyloxy-indoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346d).

I.r. spectrum (nujol):   1712 (lactam C=O);   1744 (ester C=O);   3380 (NH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.06 (3H, s, C-CH$_3$); 2.23 (3H, s,

    OCOCH$_3$); 3.36 (2H, doublet of doublets, J=15 Hz, CH$_2$); 4.5

    (1H, br. s, exchanged with D$_2$O, NH); 6.5-8.5 (8H, m, aromatic

    protons).

Mass spectrum: See Fig. 22.

Anal. Calcd. for C$_{19}$H$_{17}$N$_3$O$_3$: C, 68.05; H, 5.11; N, 12.53.

                       Found: C, 67.95; H, 5.17; N, 12.31.

(5) Acylation and sulfonation reactions:

a. Reactions with acetic anhydride

        (i) A solution of spiro[(1-hydroxyindoline)-2,4'-(3'-

methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.6 g) in acetic anhydride

(10 ml) was heated under reflux for one hour. The cooled solution

was poured into ice-cold 5% aqueous sodium hydroxide and stirred

until homogeneous. The precipitate was collected and crystallized

from ethanol to yield a pale-yellow solid (0.27 g), m.p. 306-8°

(compound A).

I.r. spectrum (nujol): 1625 and 1640 (C=O); 3410 (NH) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.63 (3H, s, CH$_3$); 4.0-5.1 (1H,

    br. s, exchanged with D$_2$O, NH); 7.2-8.3 (9H, m, aromatic

    protons).

Mass spectrum: See Fig. 4.

Anal. Calcd. for C$_{17}$H$_{13}$N$_3$O: C, 74.24; H, 4.76; N, 15.28.

                      Found: C, 74.49; H, 4.57; N, 14.98.

        The mother liquor remaining after the removal of the

above product was evaporated. The resulting reddish solid was

crystallized twice from benzene/petroleum ether (40-60°) yielding

spiro[(1,5-diacetoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-

<u>pyrazolin-5'-one)] (363)</u> as off-white crystals (0.13 g), m.p. 137-9°.

I.r. spectrum (nujol): 1667 (cyclic amide C=O); 1715 (lactam C=O);

    1760 (ester C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (DMSO-d$_6$): δ2.02 (3H, s, C$-$CH$_3$); 2.3 (3H, s,

    OCOCH$_3$); 2.50 (3H, s, NCOCH$_3$); 3.43 (2H, br. s, CH$_2$);

    7.0-8.3 (8H, m, aromatic protons).

Mass spectrum: 377 (M$^+$, 30%), 335 (31%), 293 (100%), 276 (19%),

    275 (53%), 274 (34%), 265 (21%).

Anal. Calcd. for C$_{21}$H$_{19}$N$_3$O$_4$: C, 66.83; H, 5.07; N, 11.13.

                    Found: C, 66.71; H, 5.12; N, 11.45.

        (ii) The above reaction was repeated in a mixture of

acetic anhydride (5.0 ml) and acetic acid (5.0 ml). When the reaction

mixture was allowed to cool, a pale-yellow product (0.26 g), m.p.

308-9° separated. Physical and chemical properties of this com-

pound (A') were identical to those of compound (A) except that the

i.r. spectrum of (A') had a broad absorption between 2500 and 3300

cm^{-1} (NH or OH) and a strong absorption at 1640 cm^{-1} (C=O). Mixed

m.p. of (A) AND (A') showed no depression.

        When a sample (0.2 g) of either (A) or (A') was acetylated

with acetic anhydride, it yielded an acetylated product (0.19 g), m.p.

153-4°.

I.r. spectrum (nujol): 1664 and 1730 (C=O) cm^{-1}; No NH absorption.

Mass Spectrum: 317 (M$^+$, 67%), 275 (100%), 274 (76%), 43 (48%).

Anal. Calcd. for C$_{19}$H$_{15}$N$_3$O$_2$: C, 71.98; H, 4.77; N, 13.26.

                    Found: C, 71.82; H, 4.69; N, 12.91.

        (iii) Acetylation of spiro[(1-hydroxindoline)-2,4'-(1',3'-

diphenyl-1<u>H</u>-pyrazolin-5'-one)] (0.5 g) with acetic anhydride (10 ml)

as described above gave a pale-yellow powder (0.48 g), m.p. 124-8°.
Attempted crystallization twice from ethanol/water failed to purify
this compound which was identified as spiro[(1,x-diacetyloxyindoline)-
2,4'-(1',3'-diphenyl-1$\underline{H}$-pyrazolin-5'-one)] (364).

I.r. spectrum (nujol):   1662 (cyclic amide C=O); 1725 (lactam C=O);
   1759 (ester C=O) cm^{-1};   no NH or OH absorption.

N.m.r. spectrum (DMSO-d$_6$): δ2.29 (3H, s, OCOCH$_3$);   2.45 (3H, s,
   NCOCH$_3$);   3.59 (2H, br. s, CH$_2$);   7.0-8.3 (13H, m, aromatic
   protons).

Mass spectrum: 439 (M$^+$, 16%), 397 (60%), 355 (52%), 327 (28%).

      (iv) Cold acetic anhydride (3.0 ml) was added to a
solution of the spiro (N-hydroxyindoline)pyrazolone (338, 0.3 g) in
cold pyridine (3.0 ml) and the mixture was kept for 24 hours at -10°.
A colorless crystalline solid (0.26 g), m.p. 92-3° was separated.
This was identified as spiro[(1-acetyloxyindoline)-2,4'-(3'-methyl-1'-
phenyl-1$\underline{H}$-pyrazolin-5'-one)] (349).

I.r. spectrum (nujol):   1790 (N-acetyloxy C=O);   1723 (lactam C=O)
   cm^{-1};   no NH or OH absorption.

N.m.r. spectrum (measured directly after dissolving in cold CDCl$_3$ or
   DMSO-d$_6$): δ2.05 (3H, s, CH$_3$);   2.14 (3H, s, CH$_3$);   3.38 (2H,
   doublet of doublets, J=16.5 Hz, CH$_2$);   6.5-8.2 (9H, m, aromatic
   protons).

Mass spectrum: See Fig. 26.

Anal. Calcd. for C$_{19}$H$_{17}$N$_3$O$_3$:   C, 68.05;   H, 5.11;   N, 12.53.
                       Found: C, 68.31;   H, 5.23;   N, 12.81.

      On some occasions when the above reaction was repeated,
the N-acetyloxy product (349) did not precipitate during the reaction.

When this was so, the reaction mixture was diluted with ethanol (5 ml) and poured with stirring into ice-cold water (100 ml). This yielded the spiro(N-acetoxyindoline)pyrazolone (349) as white powder (0.31 g), m.p. 90-2°. Crystallization of this powder from ethanol (or methanol) resulted in the formation of an off-white crystalline solid (0.09 g), m.p. 306-7°, the i.r. spectrum of which was identical with the previously isolated, compound (A). When the mother liquor was concentrated and allowed to stand, spiro[(5-acetyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (346d) was deposited as pale-yellow solid (0.13 g), m.p. 117-18°.

(v) Spiro[(1-hydroxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (0.3 g) was acetylated with acetic anhydride and pyridine as described above in (iv). After keeping the reaction mixture for 24 hours at 0°, it was diluted with ethanol (3 ml) and poured into ice-cold water with stirring. The white powder collected (0.32 g), m.p. 90-1° (sintered at 65°) was identified as spiro[(1-acetyloxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (361).

I.r. spectrum (nujol): 1792 (N-acetoxy C=O); 1725 (lactam C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (measured directly after dissolving in cold DMSO-d$_6$):

δ2.0 (3H, s, OCOCH$_3$); 3.6 (2H, doublet of doublets, J=16.0 Hz, CH$_2$); 6.9-9.3 (14H, m, aromatic protons).

Mass spectrum: See Fig. 26.

Anal. Calcd. for C$_{24}$H$_{19}$N$_3$O$_3$: C, 72.53; H, 4.81; N, 10.57.

Found: C, 72.19; H, 4.83; N, 10.26.

Heating the above compound (0.3 g) in ethanol produced a reddish solution. This was added, with stirring, to ice-cold water

(100 ml) and the brown precipitate formed was collected and dried.

Crystallization twice from benzene/petroleum ether (40-60°) gave a

yellow solid (0.12 g), m.p. 115-7° Which was partially identified as

<u>spiro[(x-acetyloxyindoline)-2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-</u>

<u>one)] (362).</u>

I.r. spectrum (nujol): 1723 (lactam C=O); 1750 (ester C=O); 3340

(NH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.23 (3H, s, OCOCH$_3$); 3.58 (2H,

doublet of doublets, J=15.5 Hz, CH$_2$); 5.7 (1H, br. s, exchanged

with D$_2$O, NH); 6.7-8.3 (13H, m, aromatic protons).

Anal. Calcd. for C$_{24}$H$_{19}$N$_3$O$_3$: C, 72.53; H, 4.81; N, 10.57.

Found: C, 72.11; H, 4.99; N, 10.29.

b. <u>Reaction with acetyl chloride</u>

To a solution of spiro[(1-hydroxyindoline)-2,4'-(3'-

methyl-1'-phenyl-1H-pyrazolin-5'-one)] (0.5 g) in hot dry benzene

(10 ml), acetyl chloride (1.0 ml) was added and the mixture heated

under reflux for ten hours. The resulting red solution was evaporated

to dryness, leaving a dark oil which was dissolved in hot ethanol.

Cooling gave a small quantity (0.07 g) of a product as red needles,

m.p. 209-10°. This compound remains unidentified. Its hydrolysis

is described below.

I.r. spectrum (nujol): 1688 and 1712 cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (CDCl$_3$): δ2.44 (3H, s, CH$_3$); 2.48 (3H, s, CH$_3$);

7.0-8.2 (8H, m, aromatic protons); 9.8 (1H, d, J=8 Hz, ?).

Mass spectrum: See Fig. 5.

Anal. Calcd. for C$_{19}$H$_{15}$N$_3$O$_7$: C, 68.53; H, 4.54; N, 12.61.

Found: C, 68.74; H, 4.95; N, 12.75.

After the above product was collected, the filtrate was concentrated and from it pale-orange crystals (0.3 g), m.p. 188-9° separated. This was spiro[(7-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (370).

I.r. spectrum (nujol): 1728 (C=O); 3295 (N–H) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ δ2.1 (3H, s, CH$_3$); 3.46 (2H, doublet of doublets, J=16 Hz, CH$_2$); 4.58 (1H, br. s, exchanged with D$_2$O, NH); 6.55-8.1 (8H, m, aromatic protons).

Mass spectrum: 311 (M$^+$, 100%), 294 (9%), 283 (60%).

Anal. Calcd. for C$_{17}$H$_{14}$ClN$_3$O: C, 65.49; H, 4.53; N, 13.48.

Found: C, 65.31; H, 4.66; N, 13.11.

A sample (60 mg) of this unidentified acetate, m.p. 209-10° described above was suspended in 10% aqueous sodium hydroxide (5.0 ml) and stirred for two hours. The resulting yellow solution was filtered, acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the dried (Na$_2$SO$_4$) ethereal extract yielded a yellow solid (40 mg), m.p. 179-80° (ethanol).

I.r. spectrum (nujol): 2000-3300 br. (OH); 1637 (C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ 2.58 (3H, s, CH$_3$); 4.0-5.2 (1H, br.s, exchanged with D$_2$O, OH); 8.6 (1H, d, J=8 Hz, ?); 6.7-8.1 (8H, m, aromatic protons).

Mass spectrum: 291 (M$^+$, 72%), 205 (8%), 200 (8%), 186 (10%), 178 (10%), 158 (59%), 130 (24%), 120 (100%).

Anal. Calcd. for C$_{17}$H$_{13}$N$_3$O$_2$: C, 70.1 H, 4.49; N, 14.43.

C, 69.73; H, 4.51; N, 14.02.

c. Reaction with p-chlorobenzoyl chloride

A solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-

1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (0.8 g) in dry pyridine (5.0 ml) was cooled in an ice-bath at 0-5°. $\underline{p}$-Chlorobenzoyl chloride (0.5 g) in pyridine (5.0 ml) was added dropwise with stirring. After stirring at the same temperature for one hour, the mixture was poured into ice-water to give a pale-yellow semi-solid which solidified on further cooling. The i.r. spectrum of this product displayed C=O absorptions at 1790, 1765 and 1725 cm^{-1}. A solution of this product in ether was shaken with 10% hydrochloric acid, 10% sodium carbonate, and then with water. The dried (Na_2SO_4) ethereal solution was evaporated $\underline{in}$ $\underline{vacuo}$ to yield a white solid (0.51 g). This was recrystallized from cold ethanol into colorless crystals, m.p. 196-7° identified as spiro [(x-benzoyloxyindoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (373).

I.r. spectrum (nujol): 3380 (N—H); 1732 (ester C=O); 1712 (lactam C=O) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.15 (3H, s, CH$_3$); 3.45 (2H doublet of doublets, J=17 Hz, CH$_2$); 4.47 (1H, br., exchanged with D$_2$O, NH); 6.6-8.3 (12H, m, aromatic protons).

Mass spectrum: 431 (M$^+$, 88%), 414 (2%), 403 (13%), 292 (29%), 139 (100%), 111(18%).

Anal. Calcd. for C$_{24}$H$_{18}$ClN$_3$O$_3$: C, 66.74; H, 4.20; N, 9.73.

Found: C, 66.56; H, 4.51; N, 9.98.

d. Reaction with p-toluenesulfonyl chloride

Method A: A solution of $\underline{p}$-toluenesulfonyl chloride (0.65 g) in pyridine (5 ml) was added to an ice-cold solution of 1.0 g of the spiro (N-hydroxyindoline)pyrazolone (338) in pyridine (5 ml). The mixture was stirred at 0-5° for two hours then warmed on a steam bath for

15 minutes. After cooling to room temperature, it was poured into a cold mixture of 5 ml hydrochloric acid and 100 ml water. The yellow precipitate formed was collected, and dried then dissolved in benzene. A small amount (0.09 g) of pale-yellow crystals, m.p. 306-8° separated. This was found (i.r. and mixed m.p.) to be the dehydrated compound (A) isolated earlier (p. 276). The filtrate remaining after the removal of this product was evaporated to yield a yellow solid which was difficult to crystallize. This was placed on a silica gel column and eluted with petroleum ether (30-60°) then benzene (100 ml). Evaporation of the latter solution gave a pale-yellow residue which crystallized from ethanol and yielded the previously described (p. 264) spiro[(5-chloroindoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (346a) as colorless crystals (0.18 g) m.p. 150-2°. Continued elution with chloroform (80 ml) gave a yellow oil which solidified when triturated with ethanol. Recrystallization from the same solvent gave spiro[(x-$\underline{p}$-toluene-sulfonylindoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (374) as an off-white solid (0.14 g), m.p. 162-4°.

I.r. spectrum (nujol): 1720 (C=O); 3350, br. (NH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ 2.09 (3H, s, CH$_3$); 2.45 (3H, s, CH$_3$) 3.35 (2H, doublet of doublets, J=16.5 Hz, CH$_2$); 5.0 (1H, br. s, exchanged with D$_2$O NH); 6.5-8.3 (12H, m, aromatic protons).

Mass spectrum: 447 (M+, 37%), 419 (6%), 292 (45%).

Anal. Calcd. for C$_{24}$H$_2$N$_3$O$_4$S: C, 64.61; H, 4.73; N, 9.39.

Found: C, 63.97; H, 4.89; N, 9.08.

Method B: To a stirred, ice-cold solution of the spiro(N-hydroxy-indoline)pyrazolone (338, 1.0 g) in ether (120 ml) were added dropwise

and at equal rates solutions of p-toluene sulfonyl chloride (0.65 g) in chloroform (20 ml) and triethylamine (0.35 g) in ether (15 ml). After addition, stirring was continued for two hours then the solution was filtered and concentrated to give a dark-brown semi-solid which was difficult to crystallize. When spotted on a silica gel plate and eluted with benzene/chloroform (1:2), the product was found to be a mixture of at least five compounds. This was not investigated further.

(6) Methylation:

A) **Excess** diazomethane in ether was added to a stirred solution of spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (0.8 g) in methanol (80.0 ml). After standing for 24 hours at room temperature, the solvent was removed in vacuo leaving a pale-yellow solid. Its infrared spectrum was identical to that of the starting material.

B) The above reaction was repeated in the presence of a catalytic amount (2 ml) of boron trifluoride (14% solution in methanol). The resulting green solution was allowed to stand for 24 hours at room temperature then evaporated under reduced pressure leaving a green precipitate. Crystallization of this crude product from ethanol yielded a white crystalline solid (0.68 g), m.p. 137-8°. This was found to be the previously identified (p. 274) spiro[(5-methoxy-indoline)-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (346b).

C) The reaction described above was repeated in dioxane (80.0 ml) using alcohol-free ethereal solution of diazomethane and boron trifluoride-ether complex (1 ml). Solvents were removed under reduced pressure leaving a green residue which was extracted with chloroform. Evaporation of the chloroform solution yielded a green

powder, the i.r. spectrum of which displayed a C=O absorption at 1720 cm^{-1} and no NH or OH absorption. When this solid was dissolved in ethanol, it crystallized as a dark-yellow solid (0.21 g), m.p. 308-9° identical to the unidentified compound (A) isolated earlier (p. 276). A mixed melting point of the isolated compound and compound (A) showed no depression.

      The filtrate left after isolation of the above product was concentrated to a dark semi-solid which did not crystallize. This was not investigated further.

      D) Methyl iodide (1.0 g) in methanol (5.0 ml) was added to to a solution of the spiro(N-hydroxyindoline)pyrazolone (338, 0.5 g) in methanol (15.0 ml) containing 0.2 g of sodium. The mixture was heated under reflux for three hours during which time a yellow color had developed. The solvent was evaporated and the residue extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave a yellow solid which was crystallized from methanol and yielded spiro [(1-methoxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (375) as pale-yellow crystals (0.39 g), m.p. 112-4°.

I.r. spectrum (nujol): 1719 (C=O) cm^{-1}; no NH or OH absorption.

N.m.r. spectrum (CDCl$_3$): δ1.96 (3H, s, C CH$_3$); 3.8 (3H, s, O-CH$_3$); 3.27 (2H doublet of doublet, J=17 Hz, CH$_2$); 6.8-8.3 (9H, m, aromatic protons).

Mass spectrum: See Fig. 26.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67.

                     Found: C, 70.41; H, 5.38; N, 13.29.

Preparation of 3-methyl-5-phenylpyrazolo-[4,5-c]carbostyril (350)

This compound was prepared according to the method reported by Vul'fson and Zhurin (1962) in 85% yield. M.p. 276-7° (methanol) and 275-6° (ethanol). The reported m.p. are 277-8° and 268-9° respectively.

I.r. spectrum (nujol): 1666 (C=O); 200-3220 (NH) cm^{-1}.

N.m.r. spectrum* (DMSO-d$_6$): δ2.61 (3H, s, CH$_3$); 13.2 (1H, br. s, NH or OH); 6.9-8.7 (9H, m, aromatic protons).

General Procedure for the Preparation of spiro[(1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-substituted-1',2',3',4'-tetrahydroquinolines)] (337).

A hot solution of the 4-(2-aminobenzyl)-1-phenyl-2-pyrazolone (0.5 g) in either methanol or ethanol (15.0 ml) was mixed with a quantitative amount of the appropriate aldehyde. The reaction mixture was heated under reflux for about one hour. Upon cooling, many of the title compounds separated and were recrystallized from ethanol. In some cases, the reaction mixture was concentrated to about half its volume then diluted with water. The precipitate was washed with water, dried and recrystallized from either methanol or ethanol as colorless crystals.

A similar reaction was carried out using acetone instead of an aldehyde. In this instance, the solvent used was either ethanol or butanol. Suitable reaction times were found to be 24 hours when ethanol was the solvent, or 4-6 hours when butanol was employed.

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* The n.m.r. spectrum of compound (350) crystallized from methanol had an additional methyl signal at δ3.5 which is attributed to the solvent of crystallization.
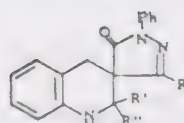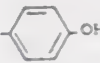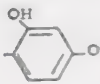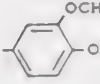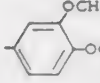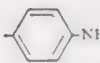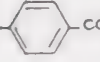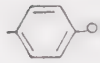
Table 6. Elemental Analyses and Physical Properties etc. of the Spiro(Tetrahydroquinoline) Pyrazolones (337a-r).

Compound	R	R'	R"	m.p. (°C)	% Yield	Molecular formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
337 a	CH_3	H	CH_3	149-50	84	$C_{19}H_{19}N_3O$	74.72	6.27	13.76	74.61	6.04	13.57
b	CH_3	H	C_2H_5	143-4	81	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	75.40	6.71	12.98
c	CH_3	H	Ph	146-7	77	$C_{24}H_{21}N_3O$	78.45	5.76	11.43	78.73	5.75	11.10
d	CH_3	H	(4-OH-phenyl)	212-3	85	$C_{24}H_{21}N_3O$	75.15	5.52	10.96	74.82	5.51	10.99
e	CH_3	H	(2-OH-phenyl)	176-8	95	$C_{24}H_{21}N_3O_2$	75.15	5.52	10.96	74.90	5.47	11.00
f	CH_3	H	(2,?-di-OH-phenyl)	180-2	73	$C_{24}H_{21}N_3O_3$	72.16	5.30	10.52	71.69	5.41	10.81
g	CH_3	H	(OCH_3, OH-phenyl)	181-2	98	$C_{25}H_{23}N_3O_3$	72.62	5.61	10.16	72.38	6.07	10.02
h	CH_3	H	(di-OCH_3-phenyl)	193-4	96	$C_{26}H_{25}N_3O_3$	73.05	5.89	9.83	72.91	5.93	9.81
i	CH_3	H	(4-NH_2-phenyl)	193-5	89	$C_{24}H_{22}N_4O$	75.37	5.80	14.65	75.44	5.73	14.13
j	CH_3	H	(2-NH_2-phenyl)	165-6	95	$C_{24}H_{22}N_4O$	75.37	5.80	14.65	75.31	5.49	14.32
k	CH_3	H	(4-COOH-phenyl)	245-6	79	$C_{25}H_{21}N_3O_3$	72.98	5.15	10.21	73.22	5.02	10.03
l	Ph	H	CH_3	174-5	93	$C_{24}H_{21}N_3O$	78.45	5.76	11.43	78.47	5.60	11.60
m	Ph	H	C_2H_5	160-2	96	$C_{25}H_{23}N_3O$	78.71	6.07	11.02	78.63	6.04	11.07
n	Ph	H	Ph	210-2	96	$C_{29}H_{23}N_3O$	81.07	5.39	9.78	81.12	5.43	9.80
o	Ph	H	(4-OH-phenyl)	237-9	95	$C_{29}H_{23}N_3O_2$	78.18	5.20	9.43	78.39	5.00	9.72
p	Ph	H	(4-COOH-phenyl)	253-4	90	$C_{30}H_{23}N_3O_3$	76.09	4.89	8.87	75.77	5.01	8.76
q	CH_3	CH_3	CH_3	148-51	90	$C_{20}H_{21}N_3O$	75.21	6.63	13.16	-	-	-
r	Ph	CH_3	CH_3	198-9	84	$C_{25}H_{23}N_3O$	78.71	6.07	11.02	78.92	5.94	10.81

The physical constants and elemental analyses of the compounds prepared by this method are compiled in Table 6. Their i.r. spectra displayed N→H absorption bands around 3400 and C=O bands around 1700 cm^{-1}. Each n.m.r. spectrum showed, in addition to the signals ascribable to the aromatic protons and the different substituents at C-3 of the tetrahydroquinoline ring, a 2-proton doublet of doublets around δ3.2 with J value ~17 Hz (CH$_2$), a one proton signal near δ4.5 (–C$\underline{H}$R) and a D-exchangeable N–H signal of variable chemical shift. Those of the 3-methylpyrazolone derivatives also contained a methyl signal around δ2.0. The mass spectra of some of these compounds were recorded and are shown in Figs. 6 and 7.

Condensation of 4-(2-aminobenzyl)-1-phenyl-2-pyrazoline-5-ones (321a, b) with formaldehyde and salicylaldehyde.

A) A mixture of 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (0.5 g) and formaldehyde (1.0 ml of 40% formalin solution) in methanol (15.0 ml) was heated under reflux for two hours. The solvent was evaporated giving an oily residue which was difficult to crystallize. The i.r. spectrum of this oil had a C=O absorption at 1707 cm^{-1} and an NH or OH absorption.

B) When 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5'-one (0.5 g) was treated similarly with formaldehyde, it yielded a white crystalline solid (0.26 g), m.p. 92-3° which was not identified. I.r. spectrum (nujol): 1710 (C=O) cm^{-1}, no NH or OH absorption. Anal. Found (Average): C, 78.27; H, 6.21; N, 8.80.

C) A solution of 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one (0.5 g) in hot ethanol (15.0 ml) was mixed with

salicylaldehyde (0.18 g). The mixture was heated under reflux for one

hour during which time its color turned dark-yellow. When cooled,

a dark-yellow solid separated. This was recrystallized from ethanol

giving 1,3-diphenyl-4[2-(o-hydroxybenzylidene)aminobenzyl]-2-

pyrazolin-5-one (385) as yellow crystals (0.55 g), m.p. 199-200°.

I.r. spectrum (nujol): 2100-3120 br. (NH and OH); 1610; 1593;

   1581; 1568 cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ3.3 (2H, doublet of doublets, J=16 Hz,

   CH$_2$); 5.3 (1H, s, CH); 6.2 (1H, br. s, exchanged with D$_2$O, NH);

   6.5-8.2 (18H, m, aromatic protons); 9.38(1H, br. s, exchanged

   with D$_2$O, OH).

Mass spectrum: See Fig. 8.

Anal. Calcd. for C$_{29}$H$_{23}$N$_3$O$_2$: C, 78.18; H, 5.20; N, 9.43.

                          Found: C, 77.98; H, 5.32; N, 9.31.

Reactions of spiro(tetrahydroquinoline)pyrazolones (337).

A. Acetylations:

        Each of the spiro(tetrahydroquinoline)pyrazolones (337b,

c, e, n and o) (0.3 g) was acetylated by heating with excess acetic

anhydride (5 ml) for 15 minutes. The reaction mixture was poured

while stirring into ice-water and the resulting product was either

collected and crystallized or extracted with ether. Ethanol was the

crystallization solvent used for all these products.

        Table 7 contains the elemental analyses of the acetylated

compounds and some of their physical constants. The i.r. spectra

of all compounds contained C=O absorption bands around 1665 (cyclic

amide) and 1710 (lactam) and were devoid of any N—H absorption.
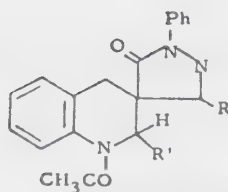
Table 7 : Elemental analyses and Physical Properties etc. of some acetylated spiro(tetrahydro-quinoline pyrazolones.

Compound	R	R'	m.p. ^oC	% Yield	Molecular formula	Analyses %		
						C	H	N
397	CH_3	C_2H_5	220-1	78	$C_{22}H_{23}N_3O_2$	Calcd. 73.11	6.41	11.63
						Found 72.79	6.28	-
395	CH_3	Ph	223-4	80	$C_{26}H_{23}N_3O_2$	Calcd. 76.26	5.66	10.26
						Found 76.59	5.60	9.91
394	CH_3	OCOCH₃-phenyl	205-6	54	$C_{28}H_{25}N_3O_4$	Calcd. 71.93	5.39	8.99
						Found 72.37	5.23	9.01
393	Ph	Ph	218-9	91	$C_{31}H_{25}N_3O_2$	Calcd. 78.96	5.34	8.91
						Found 79.01	5.33	8.87
391	Ph	phenyl-OCOCH₃	188-9	88	$C_{33}H_{27}N_3O_4$	Calcd. 74.84	5.14	7.93
						Found 74.91	5.23	7.78

Compounds (391) and (394) contained in addition a C=O band around 1765 (ester). Important signals in the n.m.r. spectra (in DMSO-d_6 or CDCl$_3$) of these acetyl derivatives are presented in Table 3 in the discussion part of this thesis.

B. Reductions:

Method A: Reduction with sodium borohydride in dioxane:

(i) A solution of spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-methyl-1',2',3',4'-tetrahydroquinoline)] (337a, 0.5 g) in dioxane (15 ml) was added dropwise to a stirred solution of sodium borohydride (0.5 g) in water (5 ml). After addition was completed, stirring was continued for thirty minutes then the reaction mixture was acidified with dilute acetic acid and diluted with water. Crystallization of the resulting precipitate from ethanol gave 4-(2-ethylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398a) as white crystalline powder (0.33 g), m.p. 181-2°.

I.r. spectrum (nujol): 2100-3500, br. (OH) with maximum at 3380 (NH); 1620 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ1.02 (3H, t, CH$_3$); 1.91 (3H, s, CH$_3$); 3.4 (2H, s, CH$_2$); 3.6 (2H, q, CH$_2$); 6.4-7.4 (11H, m, aromatic protons included 1-2 exchanged with D$_2$O, NH and pyrazolone proton).

Mass spectrum: See Fig. 9.

Anal. Calcd. for C$_{19}$H$_{21}$N$_3$O: C, 74.24; H, 6.89; N, 13.67.

Found: C, 74.11; H, 7.03; N, 13.22.

(ii) Spiro[(3-methyl-1-phenyl-1H-pyrazolin-5-one)-4,3'-(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (337b, 0.5 g) was reduced in a similar manner to yield 4-(2-n-propylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398b) as white crystals (0.31 g), m.p. 149-50°.

I.r. spectrum (nujol): 2040-3400, br. (OH) with maximum at 3380 (NH); 1617 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ0.7-1.75 (5H, m, CH$_2$CH$_3$); 2.05 (3H, s, CH$_3$); 3.3 (2H, s, CH$_2$); 3.45 (2H, t, NCH$_2$); 6.3-7.6 (10H, m, aromatic protons and pyrazoline proton); 9.02 (1H, br. s, exchanged D$_2$O, NH).

Mass spectrum: See Fig. 9.

Anal. Calcd. for C$_{20}$H$_{23}$N$_3$O: C, 74.76; H, 7.21; N, 13.07.

Found: C, 74.57; H, 7.55; N, 12.90.

(iii) Similarly, spiro[(3-methyl-1-phenyl-1$\underline{H}$-pyrazolin-5-one)-4,3'-(2'-phenyl-1',2',3',4'-tetrahydroquinoline)] (337c, 0.5 g) was reduced as described above giving 4-(2-benzylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398c) as white crystals (0.39 g), m.p. 155-6°.

I.r. spectrum (nujol): 2000-3360, br. with maximum at 3305 (N—H), 1612 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ1.88 (3H, s, CH$_3$); 3.3 (2H, s, CH$_2$); 4.25 (2H, s, CH$_2$); 6.4-7.8 (16 H, m, aromatic protons included two exchanged with D$_2$O, NH and pyrazolone ring proton).

Mass spectrum: See Fig. 9.

Anal. Calcd. for C$_{24}$H$_{23}$N$_3$O: C, 77.99; H, 6.27; N, 11.37.

Found: C, 77.56; H, 6.52; N, 10.98.

(iv) The spiro(tetrahydroquinoline)pyrazolone (337e, 0.5 g) was reduced as described above yielding a white crystalline product (0.35 g), m.p. 180-1° identified as 4-[2-(o-hydroxybenzyl)-aminobenzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one (398d).

I.r. spectrum (nujol): 2100-3300, br. (OH) with maximum at 3290 (NH);

1608 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.1 (3H, s, CH$_3$); 3.5 (2H, s, CH$_2$);

   4.33 (2H, s, CH$_2$); 6.4-8.0 (H, m, aromatic proton included

   one exchanged with D$_2$O, pyrazolone proton); 9.4 (1H, br., OH).

Anal. Calcd. for C$_{24}$H$_{23}$N$_3$O$_2$:   C, 74.78; H, 6.01; N, 10.90.

                   Found: C, 75.03; H, 6.33; N, 11.17.

Method B: Reduction with lithium aluminum hydride in ether.

        (i) A solution of the spiro(tetrahydroquinoline)pyrazolone

(337a, 0.75 g) in ether (50 ml) was slowly added, with stirring, to a

mixture of lithium aluminum hydride (0.15 g) and ether (20 ml).   After

refluxing for ten hours, water was added dropwise to the cooled reaction

mixture until the evolution of hydrogen ceased.   The solution was made

alkaline by the addition of 30% aqueous sodium hydroxide ($\sim$20 ml) then

the mixture was extracted with ether.   Evaporation of the dry (Na$_2$SO$_4$)

ether extract gave a white powder which crystallized from ethanol as a

white solid (0.14 g), m.p. 178-9°.   This compound is tentatively

identified as spiro[(3-methyl-1-phenyl-1$\underline{H}$-pyrazoline)-4,3'-(2'-methyl-

1',2',3',4'-tetrahydroquinoline)] (399a).

I.r. spectrum(nujol):   3470; 3390; 1595 cm^{-1}.

Mass spectrum: 291 (M$^+$, 2%), 263 (97%), 248 (10%), 171 (100%).

Anal. Calcd. for C$_{19}$H$_{21}$N$_3$:   C, 78.31; H, 7.21; N, 14.42.

                   Found: C, 77.97; H, 7.03; N, 13.91.

        The basic solution was neutralized with 30% sulfuric

acid then extracted with ether.   From the ethereal extract, 4-(2-ethyl-

aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398a) was

separated as off-white crystals (0.29 g), m.p. 181-2°.   Comparison

of the infrared spectrum of this compound with that of an authentic

sample prepared earlier (p. 291) proved identity.

(ii) The spiro(tetrahydroquinoline)pyrazolone (337b,
0.8 g) was reduced similarly yielding from the basic solution, a basic
product (0.12 g) as a pale-yellow solid, m.p. 170-1°.   This is tentat-
ively identified as spiro[(3-methyl-1-phenyl-1$\underline{H}$-pyrazoline)-4,3'-
(2'-ethyl-1',2',3',4'-tetrahydroquinoline)] (399b).

I.r. spectrum (nujol):   3405; 3290 br.; 1600 cm^{-1}.

Mass spectrum: 305(M$^+$, 25%), 303 (9%), 276 (13%), 274 (34%), 263

(43%), 171 (65%), 118 (100%).

Anal. Calcd. for C$_{20}$H$_{23}$N$_3$:   C, 78.65; H, 7.59; N, 13.76.

Found: C, 78.40; H, 7.61; N, 13.51.

Neutralization of the basic solution with 30% sulfuric
acid then extraction with ether yielded the 4-(2-$\underline{n}$-propylaminobenzyl)-
pyrazolone (398b) **which** crystallized from ethanol as pale-orange
needles (0.2 g), m.p. 147-8°.   The infrared spectrum of this product
was identical with that of an authentic sample of (398b) prepared
earlier (p.291).

(iii) The spiro(tetrahydroquinoline)pyrazolone (337c,
1.0 g) was reduced with lithium aluminum hydride (0.1 g) in ether as
described in preparation (i).   When the basic solution was extracted
with ether and the dried (Na$_2$SO$_4$) ether extract evaporated, a white
powder was obtained.   Fractional crystallization of this powder from
ethanol, yielded two compounds.   The infrared spectrum of the more
soluble compound (0.21 g) was identical with that of the starting
material.   The other compound (0.09 g) was recrystallized from the
same solvent giving white solid, m.p. 205-6° which is tentatively
identified as spiro[(3-methyl-1-phenyl-1$\underline{H}$-pyrazoline)-4,3'-(2'-phenyl-

1',2',3',4'-tetrahydroquinoline](399c).

I.r. spectrum (nujol): 3380; 3290, br.; 1597 cm^{-1}.

Mass spectrum: 353 (M$^+$, 7%), 351 (100%), 350 (29%), 336 (8%), 274 (22%), 193 (36%).

Accurate mass measurements: 353.1888, $C_{24}H_{23}N_3$ requires 353.1892; 351.1730, $C_{24}H_{21}N_3$ requires 351.1736.

Anal. Calcd. for $C_{24}H_{23}N_3$: C, 81.57; H, 6.56; N, 11.89.

Found: C, 81.08; H, 6.91; N, 12.03.

The basic solution was neutralized with 30% sulfuric acid then extracted with ether. Evaporation of the ethereal extract yielded off-white crystals (0.32g), m.p. 154-5° (ethanol). The infrared spectrum of this compound indicated that it was the previously identified (p. 292) 4-(2-benzylaminobenzyl)pyrazolone (398c).

Method C: Reduction with lithium aluminum hydride in tetrahydrofuran.

A solution of the spiro(tetrahydroquinoline)pyrazolone (337a, 0.75 g) in freshly distilled, dry tetrahydrofuran (30 ml) was added dropwise to a stirred solution of lithium aluminum hydride (0.15 g) in tetrahydrofuran (10 ml). The mixture was refluxed for ten hours then the solvent was removed by distillation and replaced with fresh ether (30 ml). Water was added dropwise until the evolution of hydrogen ceased. Aqueous sodium hydroxide (30%, ~10 ml) was added then the alkaline solution was extracted with ether. The ether solution was dried and evaporated to yield a white solid which was crystallized from ethanol giving white crystals (0.29 g), m.p. 179-80° identified, by infrared comparison, as the previously identified spiro-pyrazoline (399a).

Neutralization of the aqueous basic solution with dilute

hydrochloric acid followed by extraction with ether, gave a small amount (45 mg) of the previously identified 4-(2-ethylaminobenzyl)pyrazolone (398a).

Method D: Reduction by lithium aluminum hydride and aluminum chloride in ether

A method similar to that described by Nystrom and Berger (1958) was followed. A solution of granular aluminum chloride (0.67 g) in ether (20 ml) was added rapidly to a stirred solution of lithium aluminum hydride (0.19 g) in ether (20 ml). Five minutes later, a solution containing the spiro(tetrahydroquinoline)pyrazolone (337c, 1.8 g), and granular aluminum chloride (0.67 g) in ether (40 ml) was added dropwise and the mixture was refluxed for four hours. Water was added dropwise until the evolution of hydrogen ceased then the reaction mixture was made alkaline with 30% sodium hydroxide and extracted with ether. Sulfuric acid (30%) was added to the aqueous solution until it became neutral then acidic and the solution was extracted with ether each time. During acidification a solid separated out between the aqueous and organic layers. This was collected and crystallized from ethanol yielding an off-white crystalline powder (1.3 g), m.p. 155-6°. The i.r. spectrum of this product was identical with that of 4(2-benzylaminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (398c) prepared earlier (p.292). Evaporation of the ether extracts of the alkaline, neutral and acidic aqueous solutions yielded small amounts (total 0.12 g) of the same product, m.p. 155-6°. A comparison of i.r. spectra indicated identity with the compound (398c) described immediately above.

Reactions of 1,3-diphenyl-4-[2-(o-hydroxybenzylidene)aminobenzyl]-2-pyrazolin-5-one (385)

A. Attempted Reduction:

A solution of the title compound (0.5 g) in dioxane (15 ml) was added dropwise to a stirred solution of sodium borohydride (0.5 g) in water (5 ml). Stirring was continued for thirty minutes after the addition was completed then the solution was acidified with acetic acid and diluted with water. The resulting white precipitate (0.33 g) did not crystallize.

B. Methylation:

To an ice-cooled solution of the title compound (0.5 g) in dilute sodium hydroxide (15 ml), dimethylsufate (1.0 ml) was added dropwise with stirring then the mixture was heated on a water bath for one hour. The resulting oily residue was extracted with chloroform. This extract was washed with dilute sodium hydroxide then with water and dried. Evaporation of the organic solvent yielded an off-white solid (0.45 g), m.p. 128-32° which could not be purified by fractional crystallization from various solvents but which contains appreciable amounts of 1,3-diphenyl-4[2-(o-methoxybenzylidene)aminobenzyl]-2-methyl-3-pyrazolin-5-one (387).

I.r. spectrum (nujol): 1660 (C=O) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.98 (3H, s, N—CH$_3$); 3.37 (2H, s, CH$_2$); 3.87 (3H, s, OCH$_3$); 6.4-7.9 (~18H, m, aromatic protons).

Mass spectrum: 473 (M$^+$, 4%), 472 (9%), 458 (8%), 383 (80%), 118 (100%).

C. Acetylation:

The title compound (0.3 g) was heated under reflux with

acetic anhydride (5 ml) for 15 minutes then the reaction mixture was poured into ice-water (30 ml). The resulting precipitate was crystallized from ethanol yielding spiro{[1,3-diphenyl-1$\underline{H}$-pyrazolin-5-one]-4,3'-acetyl-2'-(o-acetoxyphenyl)-1',2',3',4'-tetrahydroquinoline]} (392) as colorless needles (0.22 g), m.p. 240-1°.

I.r. spectrum (nujol): 1764 (ester C=O); 1720 (lactam C=O); 1666 (amido C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ1.93 (3H, s, OCOCH$_3$); 2.24 (3H, s, NCOCH$_3$); 3.26 (2H, doublet of doublets, J=15 Hz, CH$_2$); 6.3-8.3 (14H, m, C$_2$ H and aromatic protons).

Anal. Calcd. for C$_{33}$H$_{27}$N$_3$O$_4$: C, 74.84; H, 5.14; N, 7.93.

                        Found: C, 75.21; H, 5.03; N, 7.99.

II. REDUCTIONS OF 4-(2-NITROPHENYLTHIO)-2-PYRAZOLINE-5-ONES

Preparation of 4-(2-nitrophenylthio)-2-pyrazolin-5-ones(400)

Bis-(2-nitrophenyl)disulfide

This compound was prepared from o-chloronitrobenzene (31.5 g), sodium sulfide (36 g) and sulfur (4.8 g) according to the method reported by Bogart and Stull (1928). The product was crystallized from ethanol as yellow crystals (20 g), m.p. 193-5°. Reported (Bogart and Stull, 1928) m.p. 192-5°.

2-Nitrobenzenesulfenyl chloride (404)

Was prepared following the procedure described by Hubacher (1935). Dry chlorine gas was bubbled through a warmed suspension of bis-(2-nitrophenyl)disulfide (15.4 g) and iodine (50 mg) in carbon tetrachloride (60 ml) for one to two hours. When the reaction mixture was cooled, it yielded the title compound as a yellow solid which was recrystallized from carbon tetrachloride as yellow needles (14.8 g), m.p. 73-4° as reported (Hubacher, 1935).

3-Methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a)

This compound was prepared according to the method described by Coutts et al (1966). A solution of 2-nitrobenzenesulfenyl chloride (6.0 g) in acetonitrile (40 ml) was added to a suspension of 3-methyl-1-phenyl-2-pyrazolin-5-one (6.0 g) in the same solvent (40 ml) and the mixture was stirred under reflux for four hours. When cooled, the title compound was separated as yellow crystals (9.2 g), m.p. 207-9° (decomp.) from ethanol. Reported (Coutts et al, 1966) m.p. 207°.

I.r. spectrum (nujol): 3040-3730, br. with a maximum at 3420 (OH),
1513 and 1332 (NO$_2$) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.17 (3H, s, CH$_3$); 7.1-8.5 (9H, m,
aromatic protons); 11.0-12.5 (1H, br. s, OH).

4-(2-Nitrophenylthio)-1,3-diphenyl-2-pyrazolin-5-one (400b)

Was obtained as dark yellow solid (2.9 g, m.p. 183-4°,
decomp.) from 2-nitrobenzesulfenyl chloride (1.61 g) and 1,3-diphenyl-
2-pyrazolin-5-one (2.0 g) using the same method as that described above
for the preparation of (400a). Reported (Coutts et al, 1966) m.p. 182-3°
(decomp.).

I.r. spectrum (nujol): 2100-3150, br. with maximum at 3080 (OH);
1530 and 1337 (NO$_2$) cm^{-1}

Reductions of 3-methyl-4-(2-nitrophenylthio)-1-phenyl-2-pyrazolin-5-one (400a)

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution

Following the general procedure outlined on p. 245, a
solution of the title compound (2.0 g) in 10% aqueous sodium hydroxide
(50 ml) was reduced with sodium borohydride and palladium-charcoal.
The reaction mixture was filtered and the filtrate was acidified, over
ice, with dilute acetic acid yielding a copious cream colored precipitate
(1.9 g), m.p. 140-6° (poroduct E). This product was purified by
dissolving it in dilute sodium hydroxide, filtering and acidifying the
filtrate with dilute acetic acid.

I.r. spectrum (nujol): 2200-3300, br. (OH); 3300-3400, br. (NH).

N.m.r. spectrum (DMSO-d$_6$): δ2.09 (3H, br.s, CH$_3$); 6.3-8.1 (12H,

m, aromatic protons which included   2 exchanged with D_2O).

Mass spectrum: 297 (M^+, 11%), 295 (29%), 267 (6%), 93 (100%).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$:   N, 14.13.

Found: N, 13.86.

When this compound (1.8 g) was dissolved in ethanol and filtered, a pale-yellow granular solid (0.61 g), m.p. 215-7°, precipitated during the filtration.   This product (F) was soluble in aqueous sodium hydroxide solution but insoluble in ethanol, methanol, ether, benzene or chloroform.   Acidification of the sodium hydroxide solution of (F) with acetic acid gave the ethanol-soluble product (E).   The equivalent weight of (F) was determined (by dissolving an accurately weighed quantity in a known excess of 0.1N sodium hydroxide and back titration with 0.1N hydrochloric acid using methyl orange as indicator) and was found to be 148.

I.r. spectrum (nujol):   2100-3300, br. with weak maxima at 2600, 2660 and 3070 (OH and SH); 3370 (NH); 1626 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.05 (3H, s, CH_3); 6.3-8.0 (12H, m, aromatic protons which included 2 or 3 protons exchanged with D_2O, NH, SH and pyrazolone proton).

Mass spectrum: See Fig. 10.

Accurate mass measurements: 297.0919, $C_{16}H_{15}N_3OS$ requires 297.0921; 279.0823 $C_{16}H_{13}N_3S$ requires 279.0830; 264.1138 $C_{16}H_{14}N_3O$ requires 264.1136.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13.

Found: C, 64.78; H, 4.91; N, 14.39.

Both products (E) and (F) were identified as 4-(2-mercaptophenylamino)-3-methyl-1-phenyl-2-pyrazolin-5-one (406).

[Compound erroneously identified by Pound (1970)].

When the mother liquor remaining after the removal of the above product (406) was concentrated and allowed to stand, pale-yellow needles (0.23 g), m.p. 153-4° separated. This was spiro-[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (403). Reported (Pound, 1970) m.p. 154-6°.

I.r. spectrum (nujol): 3275 (N–H); 1705 (C=O) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.22 (3H, s, CH$_3$); 4.98 (1H, br. s, exchanged with D$_2$O, NH); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: See Fig. 23.

Accurate mass measurements: See Table 5.

Anal. Calcd. for C$_{16}$H$_{13}$N$_3$OS: C, 65.06; H, 4.44; N, 14.23.

Found: C, 65.23; H, 4.18; N, 14.16.

Method B: Reduction with sodium borohydride and palladium-charcoal in dioxane

The 4-(2-nitrophenylthio)pyrazolone (400a, 2.0 g) in dioxane (80 ml) was reduced according to the general procedure (p.245). Acidification of the yellow filtrate over ice with glacial acetic acid then dilution with ice-water (300 ml) yielded a pale-brown precipitate (1.5 g). When this precipitate was dissolved in ethanol, a small amount (0.15 g) of pale-brown precipitate, m.p. 208-11° was formed. The i.r. spectrum of this product was identical to that of the thiol (406) described above. On cooling, the filtrate deposited a dark-yellow crystalline product (0.42 g), m.p. 153-5° which was identified (i.r. n.m.r. and mixed m.p.) as the spiro(benzothiazoline)pyrazolone (403).

Method C: Reduction with iron and ferrous ammonium sulfate

To a heated solution of the 4-(2-nitrophenylthio)pyrazolone

(400a, 3.0 g) in ethanol (100 ml) was added 6.0 g of reduced iron followed by a solution of ferrous ammonium sulfate (1.8 g) in water (75 ml). The mixture was heated under reflux for two hours then filtered. The filtrate was evaporated to dryness and the dried residue was dissolved in hot absolute ethanol (30 ml) then refiltered. On cooling, 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-5-one (416) separated as white needles (1.9 g), m.p. 183-4°. Reported m.p. 181° (Angelini and Martani, 1955), 183-4° (Pound, 1970).

I.r. spectrum (nujol): 2100-3350, broad with maxima at 3145 and
   3295 (OH and NH_2), 1625 (bonded C=O?) cm^{-1}.

N.m.r. spectrum (DMSO-d_6): δ2.21 (3H, s, CH_3); 6.3-8.0 (9H, m,
   aromatic protons); 7.43 (3H, br. s, exchanged with D_2O, NH_2 and
   pyrazolone proton).

Mass spectrum: See Fig. 13.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13.

Found: C, 64.91; H, 4.99; N, 13.80.

Method D: Reduction with zinc and ammonium chloride

(i) To a hot solution of the 4-(2-nitrophenylthio)pyrazolone (400a, 1.0 g) in 60% aqueous ethanol (100 ml) was added 0.2 g of ammonium chloride in water (10 ml). Zinc dust (1.0 g) was added and the mixture was refluxed for three hours under nitrogen. The reaction mixture was filtered and the solvent was evaporated in vacuo. The dried residue was dissolved in hot ethanol and refiltered. The filtrate immediately precipitated a yellow powder (0.09 g), m.p. 212-14° which was identified (i.r.) as the previously described (p. 301) thiol (406). After this product was collected, the mother liquor slowly deposited the spiro(benzothiazoline)pyrazolone (403) as dark-yellow needles (0.46 g),

m.p. 153-4°. Its i.r. spectrum was identical with that of an authentic sample prepared earlier.

(ii) When the above reduction was repeated in a mixture of tetrahydrofuran (50 ml) and water (30 ml), it yielded a small amount (0.04 g) of yellow powder, m.p. 210-2° identified as the thiol (406). On standing, the mother liquor deposited a second product (0.29 g), m.p. 152-3° which was found (i.r.) to be the spiro(benzothiazoline)pyrazolone (403).

(iii) Reaction (i) was repeated except that the mixture was stirred at room temperature for ten hours instead of heating under reflux. The filtered reaction mixture was evaporated in vacuo yielding a yellow residue which when crystallized from ethanol gave spiro[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (403) as golden-yellow needles (0.62 g), m.p. 153-4°.

Method E: Catalytic hydrogenation

(i) The title compound (1.0 g) in ethanol (250 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide ($\sim$20 mg). Hydrogen was absorbed slowly and more catalyst ($\sim$10 mg) had to be added and the reaction mixture was heated to 45°. After the uptake of hydrogen ceased, the catalyst and the yellow precipitate formed during the reaction were removed by filtration. This precipitate was dissolved in 10% sodium hydroxide, filtered and the filtrate acidified with dilute hydrochloric acid yielding a yellow powder (0.11 g) m.p. 205-10° identified (i.r.) as the thiol (406). Concentration of the filtered reaction mixture yielded another quantity (0.03 g), m.p. 207-10° of the thiol (406). On standing, the mother liquor remaining after the removal of this product slowly

deposited a pale-yellow solid (0.14 g), m.p. 151-2° which was found (i.r. and mixed m.p.) to be the spiro(benzothiazoline)pyrazolone (403).

(ii) The above reaction was repeated using "Parr" hydrogenation apparatus with initial pressure 49 p.s.i.. A small amount (0.07 g), of yellow solid was formed during the reduction; this was collected and identified (i.r.) as the 4-(2-mercaptophenyl-amino)pyrazolone (406). Evaporation of the filtered reaction mixture yielded a yellow residue which displayed absorption bands at 1700, 3300, 3270 and 3240 in its i.r. spectrum. This residue was partially soluble in dilute sodium hydroxide solution. The soluble portion, on acidification with acetic acid, yielded a small amount of white solid (0.09 g), m.p. 182-4° which was shown (i.r., mixed m.p.) to be the 4-(2-aminophenylthio)pyrazolone (416). The insoluble portion was crystallized from ethanol to yellow needles (0.23 g), m.p. 150-2° identified as the spiro(benzothiazoline)pyrazolone (403).

Reductions of 1,3-diphenyl-4-(2-nitrophenylthio)-2-pyrazolin-5-one (400b)

Method A: Reduction with sodium borohydride and palladium-charcoal in sodium hydroxide solution

Using the general procedure outlined on p. 245, a solution of the title compound (2.0 g) in 10% aqueous sodium hydroxide (50 ml) was reduced with catalyzed (10% Pd-C) sodium borohydride. Acidification of the filtrate with dilute acetic acid yielded a flocculent yellow solid. This crystallized from ethanol as a yellow solid (0.52 g), m.p. 211-12° which is identified as 1,3-diphenyl-4-(2-mercaptophenylamino)-2-pyrazolin-5-one (417). Reported (Pound, 1970), m.p. 181-4°

(Compound erroneously identified by this author).

I.r. spectrum (nujol): 2300-3400, br. with maxima at 3060 (OH and
SH); 3360 (NH); 1627 (bonded C=O?) cm^{-1}.

Mass spectrum: See Fig. 14.

Accurate mass measurements: 359.1090, $C_{21}H_{17}N_3OS$ requires
359.1090; 341.0984, $C_{21}H_{15}N_3OS$ requires 341.0987.

Anal. Calcd. $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69.

Found: C, 70.03; H, 4.86; N, 12.14.

This compound was sparingly soluble in ethanol. When
a dilute alcoholic solution was concentrated then cooled, dark-yellow
needles, m.p. 185-6° separated. This was spiro[benzothiazoline-
2,4'-(1',3'-diphenyl-1H-pyrazolin-5'-one)] (418). Reported (Pound,
1970) m.p. 183-4°.

I.r. spectrum (nujol): 3373 (NH); 1715 (C=O) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ5.0 (1H, br.s, NH); 6.5-3.3 (14H, m,
aromatic protons).

Mass spectrum: See Fig. 23.

Accurate mass measurements: See Table 5.

Anal. Calcd. for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76.

Found: C, 70.51; H, 4.28; N, 11.55.

Method B: Reduction with iron and ferrous ammonium sulfate

A solution of ferrous ammonium sulfate (0.6 g) in water
(25 ml) was added to a suspension of the 4-(2-nitrophenylthio)pyrazolone
(400b, 0.1 g) and iron (2.0 g) in ethanol (80 ml). The mixture was
heated under reflux for two hours, filtered, and evaporated to dryness
leaving a black semi-solid which could not be crystallized.

Method C: Reduction with zinc and ammonium chloride.

(i) Ammonium chloride (0.2 g) in water (10 ml) was added to a solution of title compound (1.0 g) in 60% aqueous ethanol (70 ml). To this, zinc dust (1.0 g) was added and the mixture was stirred under nitrogen for ten hours at room temperature then filtered. The filtrate was evaporated in vacuo, dissolved in hot ethanol and refiltered. Cooling yielded golden-yellow needles (0.6 g), m.p. 185-6° identified (i.r. and mixed m.p. with authentic sample) as the spiro-(benzothiazoline)pyrazoline (418) described above (p.306).

(ii) The above reaction was repeated and the mixture was refluxed under nitrogen for two hours then filtered. Evaporation of the filtrate under vacuum yielded a yellow solid, the i.r. spectrum of which had a broad absorption between 2100 and 3400 and showed no carbonyl absorption around 1700 cm^{-1}. However, when this product was dissolved in ethanol and left to crystallize it gave dark-yellow needles, m.p. 185-6° which was shown to be the spiro(benzothiazoline)-pyrazolone (418).

Reduction of spiro[benzothiazoline-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (403)

A solution of the title compound (1.0 g) in a mixture of dioxane (15 ml) and 10% aqueous sodium hydroxide (15 ml) was reduced with sodium borohydride and palladium-charcoal following the general procedure (p.245). The filtered reaction mixture was acidified over ice with dilute acetic acid and then diluted with water (50 ml). The pale-yellow precipitate was collected and dissolved in ethanol. On standing a yellow precipitate (0.13 g), m.p. 207-11° was formed. This

was identified (i.r.) as the 4-(2-mercaptophenylamino)pyrazolone (406).
Concentration of the mother liquor remaining after the removal of the
above compound yielded yellow crystals (0.36 g), m.p. 151-2° the i.r.
spectrum of which was identical with the title compound.

Reactions of 4-(2-mercaptophenylamino)-3-methyl-1-phenyl-2-
pyrazolin-5-one (406).

(1) Air Oxidation:

A sample (0.3 g) of the title compound was suspended in
ethanol (15 ml) and left exposed to the atmosphere at room temperature
for 48 hours.   During this time, it entered solution; the yellow solution
became dark-brown then dark-yellow needles (0.18 g), m.p. 153-4°
slowly separated.   This product was found (i.r., n.m.r. and mixed
m.p.) to be the spiro(benzothiazoline)pyrazolone (403).

(2) Methylation:

a. Ethereal diazomethane was added, in excess, to a
stirred, ice-cooled suspension of the title compound (1.0 g) in ether
(30 ml).   After about two hours, solubilization of products was
complete but the solution was allowed to stand for a further ten hours
at room temperature, then the rose-red solution was evaporated under
vacuum leaving a reddish oily residue, which crystallized from methanol
to yellow needles (0.58 g), m.p. 150-1°.   Its infrared and n.m.r.
spectra were identical to those of the previously identified spiro[benzo-
thiazoline-2,4'-(3'-methyl-1'-phenyl-1$\underline{H}$-pyrazolin-5'-one)] (403).

b. Dimethyl sulfate (1.0 ml) was added dropwise with
stirring to an ice-cold solution of the 4-(2-mercaptophenylamino)-
pyrazolone (406, 1.0 g) in 10% sodium hydroxide.   After stirring for
two hours, the resulting gummy residue was extracted with chloroform

and the chloroform solution was washed with 10% sodium hydroxide then with water. Evaporation of the dried ($CaCl_2$) extract gave a brown solid which crystallized from ethanol yielding 2,3-dimethyl-4-(2-methylthio-phenylamino)-1-phenyl-2-pyrazolin-5-one (408) as pale-brown needles (0.47 g), m.p. 161-2°.

I.r. spectrum (nujol): 3335 (NH); 1670 (C=O) cm^{-1}.

N.m.r. spectrum:($CDCl_3$): δ2.14 (3H, s, C CH_3); 2.39 (3H, s, S CH_3); 3.03 (3H, s, N CH_3); 6.12 (1H, br. s, exchanged with D_2O, NH); 6.4-7.6 (9H, m, aromatic protons).

Mass spectrum: See Fig. 11.

Accurate mass measurements: 325.1240, $C_{18}H_{19}N_3OS$ requires 325.1249; 278.1287, $C_{17}H_{16}N_3O$ requires 278.1293.

Anal. Calcd. for $C_{18}H_{19}N_3OS$: C, 66.46; H, 5.85; N, 12.92.

Found: C, 66.83; H, 6.16; N, 12.68.

(3) Benzoylation:

was carried out according to the method described by Pound (1970). Benzoyl chloride (2.0 ml) was added dropwise, with stirring to an ice-cold solution of the title compound (1.0 g) in 10% sodium hydroxide (40 ml). Stirring was continued at room temperature for one hour then the resulting semi-solid was extracted with chloro-form. Evaporation of the dried ($CaCl_2$) extract left a dark-yellow semi-solid which was difficult to crystallize. This was placed on a silica gel column and eluted with benzene/chloroform (1:2) yielding a fraction which, on evaporation, gave a brown solid (0.61 g). This was crystallized twice from benzene/petroleum ether (40-60°) and gave 4-[N-benzoyl-N-(benzoylthiophenyl)amino]-5-benzoyloxy-3-methyl-1-phenylpyrazole (414) as pale-brown solid, m.p. 104-7°. Reported

(Pound, 1970) m.p. 102-4° (Compound erroneously identified by this author).

I.r. spectrum (nujol): 1758 and 1679 (C=O) cm^{-1}.

Mass spectrum: See Fig. 12.

Accurate mass measurements: 609.1724, $C_{37}H_{27}N_3O_4S$ requires
609.1723.

Anal. Calcd. for $C_{37}H_{27}N_3O_4S$: C, 72.89; H, 4.46; N, 6.89.

Found: C, 72.67; H, 4.51; N, 6.99.

(4) Acetylation:

a. A suspension of the 4-(2-mercaptophenylamino) pyrazolone (406, 0.5 g) in acetic anhydride (5 ml) was heated under reflux for fifteen minutes. The resulting red solution was poured, with stirring, into ice-cold 5% sodium hydroxide solution (30 ml) giving a brown precipitate. This was extracted with chloroform and the chloroform extract was washed with 10% sodium carbonate then with water and dried ($CaCl_2$). Evaporation of this extract yielded a brown oil which crystallized from ethanol into dark-yellow crystals (0.19 g), m.p. 150-1°, the i.r. of which was identical with the spiro (benzothiazoline)pyrazolone (403).

b. Acetyl chloride (2.0 ml) was added to a suspension of the 4-(2-mercaptophenylamino)pyrazolone (406, 0.5 g) in benzene (15 ml) and the mixture was refluxed for one hour then evaporated under vacuum. Crystallization of the dark-red semi-solid yielded the spiro(benzothiazoline)pyrazolone (403) as dark-yellow needles (0.22 g), m.p. 153-4°.

c. The 4-(2-mercaptophenylamino)pyrazolone (406, 0.5 g) was added to a cold mixture of pyridine (5.0 ml) and acetic anhydride

(5.0 ml) and stirred for fifteen minutes. The resulting solution was added with stirring to ice-cold water (40 ml) giving a yellow precipitate (0.46 g), m.p. 104-10° identified as <u>5-acetyloxy-3-methyl-4-(2-acetyl-thiophenylamino)-1-phenylpyrazole (415)</u>. This compound was insoluble in dilute sodium hydroxide solution.

I.r. spectrum (nujol): 3368 (N—H); 1788 (OCOCH$_3$); 1720 (SCOCH$_3$) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): δ2.15 (3H, s, CH$_3$); 2.22 (3H, s, CH$_3$); 2.44 (3H, s, CH$_3$); 6.2 (1H, br. s, NH); 6.5-8.2 (9H, m, aromatic protons).

Mass spectrum: 381 (M$^+$, 3%), 339 (17%), 321 (3%), 297 (20%), 295 (64%), 279 (30%), 267 (75%), 135 (100%).

Anal. Calcd. for C$_{20}$H$_{19}$N$_3$O$_3$S: C, 62.97; H, 5.02.

Found: C, 63.53; H, 4.89.

Attempts to crystallize the above compound from ethanol yielded, after about 24 hours standing, a yellow crystalline solid m.p. 152-4° which was found (i.r.) to be the spiro(benzothiazoline)pyrazolone (403).

<u>General procedure for the preparation of spiro[(3-substituted-3,4-dihydro-2<u>H</u>-1,4-benzothiazine)-2,4'-(3'-methyl-1'-phenyl-1<u>H</u>-pyrazolin-5'-ones)] (419)</u>

Equimolar quantities of 4-(2-aminophenylthio)-3-methyl 1-phenyl-2-pyrazoline-5-one (416) and the appropriate aldehyde were heated, under reflux, in ethanol for one to two hours. The reaction of (416) and acetone was carried out in n-butanol and heating was prolonged to 24 hours. Most products crystallized from the reaction solvent on cooling.

Table 8 collects the physical constants and elemental analyses of the compounds prepared by this method. The i.r. spectra of all these compounds displayed N—H absorption bands around 3400 and C=O bands around 1700 cm^{-1}. Their n.m.r. spectra (in DMSO-d$_6$) had signals ascribable to the pyrazolone C-3 methyl group (around $\delta 2.0$), the aromatic protons and the different substitutents at C-3 of the dihydro-benzothiazine ring. In addition, each spectrum (except that of the 3,3-di-methyl derivative 419n) contained a one proton signal near $\delta 4.8$ ($-\overset{|}{\underset{}{C}}HR$) and a deuterium-exchangeable N—H signal of variable chemical shift. Both the pyrazolone C-3 methyl group and the hydrogen at C-3 of the dihydrobenzothiazine ring appeared as two signals separated by from 3 Hz (419 e, R'=p-hydroxyphenyl) to 14 Hz (419b, R'=CH$_2$CH$_3$). This separation was absent in compounds 419c, R'=COCH$_3$ and (419n, R=R'= CH$_3$). The mass spectra of some of these compound were recorded (see Fig. 15 and 16 and Table 4).

Attempts to separate the positional isomers of compound 419l (R=H, R'=o-nitrophenyl) by fractional crystallization failed.

Acetylation of two spiro(dihydrobenzothiazine)pyrazolones:

The spiro(dihydrobenzothiazine)pyrazolones, 419h (R=H, R'=2,5-dimethoxyphenyl) and 419e (R=H, R'=p-hydroxyphenyl) were acetylated by heating with acetic anhydride for 15 minutes. Compound 419h produced a monoacetyl derivative, m.p. 214-5°.

I.r. spectrum (nujol): 1665 (amide C=O); 1708 (lactam C=O) cm^{-1}.

N.m.r. spectrum (CDCl$_3$): $\delta 1.0$ (3H, s, C—CH$_3$); 2.22 (3H, s, COCH$_3$); 3.38 (3H, s, OCH$_3$); 3.70 (3H, s, OCH$_3$); 6.67-8.2((13H, m, C$_3$—H and aromatic protons).

(419)
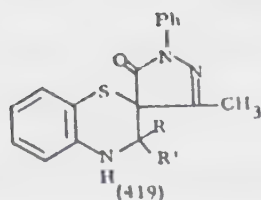
Table 8: Elemental analyses and physical properties ...etc. of the spiro(dihydrobenzothiazoline)-

pyrazolones (419a-n).

Compound	R	R'	m.p. °C	% Yield	Molecular formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	H	CH₃	149-50	76	$C_{16}H_{17}N_3OS$	66.84	5.29	12.99	66.63	5.44	12.75
b	H	C₂H₅	118-20	88	$C_{19}H_{19}N_3OS$	67.61	5.68	12.45	67.32	5.64	12.25
c	H	COCH₃	144-5	77	$C_{19}H_{17}N_3O_2S$	64.93	4.87	11.95	64.67	4.94	12.24
d	H	Ph	157-8	90	$C_{23}H_{19}N_3OS$	71.66	4.97	10.90	72.02	5.05	11.3
e	H	⬡OH	225-7	65	$C_{23}H_{19}N_3O_2S$	68.80	4.77	10.46	68.75	4.89	10.56
f	H	⬡OCH₃	137-8	66	$C_{24}H_{21}N_3O_2S$	69.37	5.09	10.11	69.09	5.09	9.72
g	H	⬡(OCH₃)OH	172-3	63	$C_{24}H_{21}N_3O_3S$	66.81	4.91	9.74	66.82	4.78	9.95
h	H	H₃CO⬡OCH₃	129-30	90	$C_{25}H_{23}N_3O_3S$	67.39	5.20	9.43	67.36	5.58	9.18
i	H	⬡(OCH₃)(OCH₃)	185-6	86	$C_{25}H_{23}N_3O_3S$	67.39	5.20	9.43	67.57	5.30	9.22
j	H	⬡COOH	134-5	84	$C_{24}H_{19}N_3O_3S$	67.10	4.46	9.80	67.31	4.29	9.61
k	H	⬡Cl	150-1	72	$C_{23}H_{18}ClN_3OS$	65.85	4.32	10.01	65.86	4.46	10.12
l	H	O₂N⬡	187	92	$C_{23}H_{18}N_4O_3S$	64.17	4.21	13.01	64.31	4.29	13.09
m	H	⟨furyl⟩	139-40	65	$C_{21}H_{14}N_3OS$	67.17	4.56	11.21	66.84	4.71	11.10
n	CH₃	CH₃	155-6	61	$C_{19}H_{19}N_3OS$	67.61	5.68	12.45	67.61	5.61	12.36

Anal. Calcd. for $C_{27}H_{25}N_3O_3S$: C, 68.76; H, 5.34; N, 8.91.

Found: C, 68.98; H, 5.69; N, 9.03.

Compound 419e gave a diacetylated product, m.p. 183-4°.

I.r. spectrum (nujol): 1768 (ester C=O); 1710 (lactam C=O); 1674 and

1660, doublet (amide C=O) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ0.98 (3H, s, C–CH$_3$); 2.14 (3H, s,

OCOCH$_3$); 2.22 (3H, s, N–COCH$_3$); 6.6 (1H, s, CH); 7.0-8.2

(13H, m, aromatic protons).

Anal. Calcd. for $C_{27}H_{23}N_3O_4S$: C, 66.79; H, 4.77; N, 8.65.

Found: C, 66.88; H, 4.72; N, 8.30.

Condensation of 4-(2-aminophenylthio)-3-methyl-1-phenyl-2-pyrazolin-
5-one (416) with formaldehyde, salicylaldehyde and 2,4-dihydroxybenz-
aldehyde.

A. Formaldehyde (1.0 ml of 45% solution in water) was

added to a hot solution of the title compound (0.5 g) in methanol (5 ml)

and the mixture was refluxed for one hour. Evaporation of the solvent

gave a colorless oil which would not crystallize.

I.r. spectrum (thin film): 1710 (C=O) cm^{-1}; no NH or OH absorption.

B. A mixture of the title compound (1.0 g) and salicyl-

aldehyde (0.41 g) in ethanol (30 ml) was heated under reflux for one

hour during which time a yellow precipitate was formed. Crystallization

of this precipitate from ethanol yielded a yellow solid (1.15 g), m.p.

232-3° identified as 4-[2-(o-hydroxybenzylidene)aminophenylthio]-3-

methyl-1-phenyl-2-pyrazolin-5-one (425a).

I.r. spectrum (nujol): 2000-3300, broad (OH); 1612 (C=N) cm^{-1}.

N.m.r. spectrum (DMSO-d$_6$): δ2.2 (3H, s, CH$_3$); 5.4 (1H, s, CH);

6.3-8.0 (13H, m, aromatic protons and pyrazolone proton); 8.82 (1H, br. s, exchanged with D_2O, OH); 9.84 (1H, br. s, exchanged with D_2O, OH).

Anal. Calcd. for $C_{23}H_{19}N_3O_3S$: C, 66.17; H, 4.59; N, 10.07.

Found: C, 66.47; H, 4.12; N, 9.66.

III.   1-HYDROXY-2-PHENYL-1,2-DIHYDROPYRIDINE AND
BENZOYL DERIVATIVE

1-Hydroxy-2-phenyl-1,2-dihydropyridine (255)

This compound was prepared by the interaction of pyridine 1-oxide (2.8 g) and phenylmagnesium bromide (7.9 g) in tetrahydrofuran (15 ml) according to the method described by Kato and Yamanaka (1965).   Crystallization from benzene yielded the title compound as pale-yellow needles (3.1 g), m.p. 132° as reported (Kato and Yamanaka, 1965).

I.r. spectrum (nujol):   3400-2400 (N—OH) cm^{-1}.

N.m.r. spectrum (CDCl$_3$):   The N—OH proton appeared at δ8.72 and disappeared when D$_2$O was added.

Mass spectrum: See Fig. 24.

Anal. Calcd. for C$_{11}$H$_{11}$NO: C, 76.27; H, 6.40; N, 8.09.

Found: C, 76.26; H, 6.18; N, 8.12.

1-Benzoyloxy-2-phenyl-1,2-dihydropyridine (437)

Was prepared according to the method of Kato et al (1967) in 90% yield, m.p. 79-80°.   Reported m.p. 78.5-79.5°.

I.r. spectrum (nujol):   1755 (C=O) cm^{-1}.

Mass spectrum: See Fig. 24.

Anal. Calcd. for C$_{18}$H$_{15}$NO$_2$:   C, 77.96; H, 5.45; N, 5.05.

Found: C, 77.71; H, 5.41; N, 5.06.

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